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For the Study of the Circulation

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American Heart Journal

VOL. 23 MARCH, 1942 No. 3

Original Communications

FURTHER STUDIES IN IMMUNIZATION AGAINST RHEUMATIC FEVER

VALENTINA P. WASSON, M.D., AND EDWARD E. BROWN, M.D.
NEW YORK, N. Y.

IN JULY, 1940, we[1] reported the results of immunization against recurrences of acute rheumatic fever in thirty-one children who were known to have rheumatic heart disease, or to be potential cardiac patients. A follow-up study of thirty-five other patients who had received the same treatment elsewhere was included.

In September, 1939, we began to immunize a new group of forty-three cardiac children by the same method, and in September, 1940, we added another group of forty-two rheumatic cardiac patients who have been given a modified form of treatment. This paper includes a survey of these two groups and of a control group and also a follow-up study of sixty-six previously treated patients, with their corresponding control groups.

The treatment that forty-three children began to receive in September, 1939, and that lasted for two consecutive winters, consisted of repeated injections of graduated doses of hemolytic streptococcus filtrate (N. Y. 5 strain). The preparation of the filtrate and the procedure of immunization were given in detail by us[2] in 1939. Here we shall report only on the present progress of treatment.

For the sake of clarity the data obtained from the group of patients who began treatment in 1939 will be discussed in two stages, namely, the results of the first winter, and the results of the second winter, in each case in comparison with the respective control group. The distinction between the two years is necessary because the control patients were not the same in both years. The same observation applies to

This work was carried out at the New York Post-Graduate Hospital and Medical School under the auspices of the Department of Pediatrics, and it was financed by the John and Mary R. Markle Foundation.

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formerly treated patients who have been followed carefully in the clinic and whose health has to be compared with that of patients who have never had any specific treatment.

The original group of patients in the fall of 1939 consisted of forty-three rheumatic cardiac and potential cardiac children, of whom sixteen were males, and twenty-seven, females. Their mean age was 11.6 years (Table I). The average number of reported colds per child was 3.6 for the first winter, and the average gain in weight, 5.7 pounds. Among subacute rheumatic complaints, abdominal symptoms were reported frequently by six patients; chronic pallor, by nine; epistaxis on more than two occasions, by three; joint and muscle pains, by six; cardiac symptoms, such as dyspnea and precordial pain, by five; headaches, by eighteen; and twitching, by five. There were three attacks of acute rheumatic fever. To aid in diagnosis we used the erythrocyte sedimentation rate, the hemoglobin estimation, and the Schilling and platelet counts on all patients. The laboratory procedure which we employed was described by us recently.[3]

In 1939 to 1940 the mean laboratory values for the treated group were: erythrocyte sedimentation rate, 9.6 mm. per hour;* hemoglobin, 72.2 per cent; nonfilamented cell count, 11.4 per cent; and platelet count, 179,000 per cubic millimeter.

In the past, under "Results," we gave our opinion of the patient's rheumatic state at the end of each year. In this paper we give our opinion of the patient's condition at the beginning of each year, e.g., September, and at the end, e.g., late June. These opinions are based on careful clinical and laboratory data for each patient.†

The control group for the same year comprised forty-five patients, of whom twenty-nine were males, and sixteen, females. The average age was approximately the same as in the treated group. The control group showed fewer colds and more gain in weight than the treated group. The subacute rheumatic symptoms were much more troublesome in the untreated group, and there were nineteen attacks of rheumatic fever, chorea, and carditis, together with one death. Twelve of the nineteen were hospitalized.

In September, 1940, only thirty-five children started the second year of treatment, for four had moved away, two had decided that they were too well to continue the injections, one could not be traced, and one was transferred to a group which was receiving a modified form of treatment, to be described below.

The group of thirty-five who continued treatment was made up of twelve boys and twenty-three girls whose average age was 11.7 years

*Linzenmeier—Rounert microsedimentation method was used.

†We have not used the therapeutic classification established by the New York Heart Association because it was introduced during the course of our observations, and, at least initially, the application of the new classification was not uniform among the physicians at the clinics.

TABLE I

COMPARISON BETWEEN TREATED AND CONTROL PATIENTS DURING 1939-1940

	TREATED		CONTROL	
No. of patients	43		45	
Sex	16 males; 27 females		29 males; 16 females	
Av. age (yr.)	11.6		11.5	
No. of reported colds per child	3.6		2.3	
Mean weight gain (lb.)	5.7		7.5	
Abdominal symptoms				
+	13		9	
++	1		3	
+++	6		6	
Pallor				
+	6		5	
++	2		7	
+++	9		11	
Epistaxis				
+	8		2	
++	1		4	
+++	3		3	
Rheumatic pains				
+	5		7	
++	11		7	
+++	6		12	
Cardiac symptoms				
+	7		6	
++	3		8	
+++	5		6	
Headaches				
+	3		4	
++	3		7	
+++	18		11	
Twitching				
+	4		3	
++	3		1	
+++	5		7	
No. of attacks of rheumatic fever, carditis, and chorea	3, or 7%		19, or 40.2%	
Deaths	0		1	
Mean laboratory data:				
E.S.R. (mm. per hr.)	9.6		12.5	
Hemoglobin (%)	72.2		73.4	
Nonfilamented neutrophiles (%)	11.4		9.3	
Platelets (per cu. mm.)	179,000		186,000	
Estimation of patient's condition:	*Fall (1939)*	*Spring (1940)*	*Fall (1939)*	*Spring (1940)*
Excellent	5	10	14	12
Very good	5	11	9	7
Good	9	9	4	3
Av.	11	8	6	3
Fair	10	2	5	1
Poor	3	3	7	19

Symbols: +, occurred once; ++, occurred twice; +++, occurred more than twice.

TABLE II

COMPARISON BETWEEN TREATED AND CONTROL PATIENTS DURING 1940-1941

	TREATED	CONTROL
No. of patients	35	33
Sex	12 males; 23 females	17 males; 16 females
Av. age (yr.)	11.7	12.1
No. of reported colds per child	3	2.9
Mean weight gain (lb.)	9.2	7.9
Abdominal symptoms		
+	9	4
++	2	4
+++	3	5
Pallor		
+	9	3
++	1	1
+++	4	12
Epistaxis		
+	4	3
++	4	4
+++	1	0
Rheumatic pains		
+	8	3
++	2	3
+++	4	14
Cardiac symptoms		
+	4	5
++	2	1
+++	3	10
Headaches		
+	7	1
++	2	1
+++	6	11
Twitching		
+	1	2
++	2	2
+++	2	4
No. of attacks of rheumatic fever, carditis, and chorea	4, or 11.4%	11, or 33%
Deaths	0	3
Mean laboratory data:		
E.S.R. (mm. per hr.)	9.4	17
Hemoglobin (%)	74.3	73.2
Nonfilamented neutrophiles (%)	8	10.5
Platelets per cu. mm.	200,000	192,000

Estimation of the patient's condition:	*Fall (1940)*	*Spring (1941)*	*Fall (1940)*	*Spring (1941)*
Excellent	9	14	10	8
Very good	11	10	4	2
Good	8	3	5	4
Av.	7	2	5	4
Fair	1	2	5	4
Poor	0	4	4	11

Symbols: +, occurred once; ++, occurred twice; +++, occurred more than twice.

(Table II). The average number of upper respiratory infections was three for twelve months (June, 1940, to June, 1941), and the mean gain in weight for the same period was 9.2 pounds per child. The subacute rheumatic symptoms abated markedly during the second winter of treatment; considerably fewer patients showed pallor, abdominal symptoms, epistaxis, and joint and muscle pains. Chronic headaches, which were present in eighteen patients during the first winter of treatment, were troublesome only in six children. Four patients, or 11.4 per cent, suffered one attack each of acute rheumatic fever. The laboratory data showed little change from the preceding year. However, the nonfilamented neutrophile count dropped to normal, and the platelet count showed a moderate increase.

The control group during the second year of treatment consisted of thirty-three patients. Twenty of these were carried over from the preceding year, and the rest were newcomers in September, 1940.

There were seventeen boys and sixteen girls in this group (Table II). Their average age was 12.1 years. The number of reported colds per child was 2.9, and the mean gain in weight, 7.9 pounds. The subacute rheumatic fever symptoms were many and severe, except for the absence of nosebleeds. There were eleven attacks of rheumatic fever, with three deaths.

Formerly Treated Group.—In order to estimate the more remote effects of this form of immunization against rheumatic fever, the group of patients who were treated from 1937 to 1939 was carefully followed in the cardiac research clinic. They received the same attention as the control patients. It is only natural that, with the passing of time, this group has dwindled somewhat. Of thirty-one patients, six failed to return for follow-up study after they had been told that they had received their last "needle." Four patients who had attended the clinic regularly also vanished. Therefore, twenty-five of thirty-one formerly treated patients have been observed regularly during 1939 to 1940, and twenty-one of those, during 1940 to 1941. The regularity of their attendance was excellent.

The condition of the twenty-five formerly treated patients who attended the clinic during 1939 to 1940 is compared with that of the already discussed control group of forty-five patients for that year, and the twenty-one formerly treated patients who were observed during 1940 to 1941 are compared with the control group of thirty-three children.

Naturally, the formerly treated patients are considerably older than those with whom they are being compared from year to year. The clinic is not large enough to carry separate control groups for formerly and presently treated patients. The control group varies from year to year partly because untreated patients are less well disciplined with respect to regular attendance, partly because many ask to be immunized and

join the new groups who are getting treatment, and partly because we are trying now to make them similar in age and severity of heart disease with the groups that receive active treatment. In the latter a few patients may drop out in the course of treatment, but after the first months no new ones are taken. Thus the treated groups remain constant in composition, and the control group is constant in age.

The Follow-up Study of Formerly Treated Patients.—In 1939 to 1940 the mean age of the twenty-five formerly treated patients was 14.8 years (Table III). The mean gain in weight for the twelve months was 7.25 pounds, and the average number of reported upper respiratory infections was two. Among frequent subacute symptoms, abdominal distress occurred in two patients; bodily pains, in three; dyspnea and precordial pain, in one; and headaches in four. There were three attacks (12 per cent) of acute rheumatic fever. The average hematologic observations were all within normal limits.

The average age of forty-five control patients for the same period was 11.5 years. Their average gain in weight and the number of reported colds were approximately the same as in the group just mentioned. Among frequent subacute symptoms, abdominal pain and vomiting occurred in six; pallor in eleven; epistaxis in three; rheumatic pains in twelve; cardiac symptoms in six; headaches in eleven; and twitching in seven. There were nineteen instances (40.2 per cent) of acute rheumatic fever attacks, with one death. The mean sedimentation rate was 4.5 mm. per hour higher, and the nonfilamented neutrophile count 1.3 per cent higher.

During the winter of 1940 to 1941 the remaining twenty-one formerly treated patients fared even better (Table IV). The gain in weight for the year was 8.45 pounds. Only two complained of chronic abdominal symptoms; one showed chronic pallor; two had many nosebleeds, two had frequent joint and muscle pains; and two had chronic headaches. Only one patient (4.76 per cent) developed an attack of rheumatic fever. The average blood picture was normal.

A comparison with the control group of thirty-three patients in the same year shows that, although the gain in weight and the average number of colds were about the same, the subacute rheumatic fever symptoms in the control group were distressingly high; also, there were eleven acute rheumatic fever attacks, with three deaths.

In our effort to delve still further into the effects of immunization against rheumatic fever over a period of years, we have been fortunate in receiving permission* to examine and question all available patients who were under study prior to 1937. We first reported on their condition in June, 1939.[1] The second "round-up" of this group took place in June, 1941.

*Courtesy of Flower-Fifth Avenue Hospital.

TABLE III

COMPARISON BETWEEN FORMERLY TREATED AND CONTROL PATIENTS IN 1939-1940

	FORMERLY TREATED		CONTROL	
No. of patients	25		45	
Sex	16 males; 9 females		29 males; 16 females	
Av. age (yr.)	14.8		11.5	
No. of reported colds per child	2		2.3	
Mean weight gain (lb.)	7.25		7.5	
Abdominal symptoms				
+	7		9	
++	0		3	
+++	2		6	
Pallor				
+	0		5	
++	2		7	
+++	2		11	
Epistaxis				
+	2		2	
++	1		4	
+++	0		3	
Rheumatic pains				
+	1		7	
++	2		7	
+++	3		12	
Cardiac symptoms				
+	1		6	
++	0		8	
+++	1		6	
Headaches				
+	2		4	
++	1		7	
+++	4		11	
Twitching				
+	0		3	
++	0		1	
+++	0		7	
No. of attacks of rheumatic fever, carditis, and chorea	3, or 12%		19, or 40.2%	
Deaths	0		1	
Mean laboratory data:				
E.S.R. (mm. per hr.)	8		12.5	
Hemoglobin (%)	74		73.4	
Nonfilamented neutrophiles (%)	8		9.3	
Platelets per cu. mm.	185,000		186,000	
Estimation of patient's condition:	*Fall (1939)*	*Spring (1940)*	*Fall (1939)*	*Spring (1940)*
Excellent	12	16	14	12
Very good	6	4	9	7
Good	4	0	4	3
Av.	1	2	6	3
Fair	1	0	5	1
Poor	1	3	7	19

Symbols: +, occurred once; ++, occurred twice; +++, occurred more than twice.

TABLE IV

COMPARISON BETWEEN FORMERLY TREATED AND CONTROL PATIENTS IN 1940-1941

	FORMERLY TREATED		CONTROL	
No. of patients	21		33	
Sex	13 males; 8 females		17 males; 16 females	
Av. age (yr.)	15.8		12.1	
No. of reported colds per child	2.2		2.9	
Mean weight gain (lb.)	8.45		7.9	
Abdominal symptoms				
+	2		4	
++	0		4	
+++	2		5	
Pallor				
+	1		3	
++	1		1	
+++	1		12	
Epistaxis				
+	2		3	
++	1		4	
+++	2		0	
Rheumatic pains				
+	5		3	
++	0		3	
+++	2		14	
Cardiac symptoms				
+	2		5	
++	0		1	
+++	0		10	
Headaches				
+	1		1	
++	3		1	
+++	2		11	
Twitching				
+	1		2	
++	0		2	
+++	0		4	
No. of attacks of rheumatic fever, carditis, and chorea	1, or 4.76%		11, or 33%	
Deaths	0		3	
Mean laboratory data:				
E.S.R. (mm. per hr.)	9.6		17	
Hemoglobin (%)	77		73.2	
Nonfilamented neutrophiles (%)	7.4		10.5	
Platelets per cu. mm.	180,000		192,000	
Estimation of the patient's condition:	*Fall (1940)*	*Spring (1941)*	*Fall (1940)*	*Spring (1941)*
Excellent	12	12	10	8
Very good	4	6	4	2
Good	0	1	5	4
Av.	2	1	5	4
Fair	0	0	5	4
Poor	3	1	4	11

Symbols: +, occurred once; ++, occurred twice; +++, occurred more than twice.

TABLE V

COMPARISON BETWEEN FORMERLY TREATED AND CONTROL PATIENTS IN 1939-1941

	FORMERLY TREATED (1933-35-37)		CONTROL	
No. patients	22		12	
Sex	14 males; 9 females		6 males; 6 females	
Av. age	13.2		15	
No. of reported colds per child	1.6		3	
Av. gain in weight (lb.) (2 yr.)	23.5		13.9	
Abdominal symptoms				
+	0		1	
++	1		2	
+++	1		1	
Pallor				
+	0		0	
++	0		0	
+++	0		1	
Epistaxis				
+	0		0	
++	2		0	
+++	0		2	
Joint pains				
+	5		0	
++	1		2	
+++	1		4	
Cardiac symptoms				
+	1		1	
++	0		0	
+++	1		4	
Headaches				
+	4		0	
++	0		2	
+++	1		3	
Twitching				
+	0		0	
++	0		2	
+++	0		0	
Attacks of rheumatic fever	1, possibly 2		3	
Estimation of the patient's condition:	*Spring (1939)*	*Spring (1941)*	*Spring (1939)*	*Spring (1941)*
Excellent	12	11	1	1
Very good	5	4	1	1
Good	2	3	2	3
Av.	1	2	2	1
Fair	0	1	2	3
Poor	2	1	4	3

Symbols: +, occurred once; ++, occurred twice; +++, occurred more than twice.

Of the original group of thirty-five treated patients, eighteen reappeared four years later for re-examination. Four did not come, although their recent cardiac clinic records were available, and thus they may be included here. The remaining thirteen have been dropped, either because of age or change of residence, and they could not be traced.

Hence we have the record of twenty-two patients, which is, needless to say, a brief one, for the only sources were the relatively infrequent entries in the cardiac charts (thanks to the children's good health), the memory of the patients and their relatives, and a physical examination by one of us. Blood cell counts and sedimentation rates were performed only when needed, and, since this group, with one exception, enjoyed excellent health, they are too few for statistical appraisal. The clinical record is as follows (Table V): In this group of formerly treated patients whose records are up to date there were nine girls and fourteen boys. Their mean age in June, 1941, was 13.2 years. The average gain in weight was 23.5 pounds per child over twenty-four months. The number of colds reported was 1.6 per patient for two years, which is probably too low because of forgetfulness, and the tendency of the older children, when unaccompanied by their parents, to lean toward optimism. Among the subacute symptoms which were remembered by them over a two-year period or were recorded in the New York Heart Association charts, the following occurred more than twice: abdominal pain and vomiting in one, joint and muscle pains in one, cardiac symptoms in one, and headaches in one. One attack of rheumatic fever and one attack of "abdominal grippe" which lasted for a week were recorded. But since the latter patient now shows not only mitral insufficiency and stenosis but also aortic insufficiency, it is safe to assume that he suffered an attack of acute rheumatism in which abdominal symptoms were prominent and joint pains absent.

The corresponding control group yielded information about twelve patients, eight of whom appeared for examination; the recent records of four others are available. Of this group, six were boys and six girls. Their average age at the time of their visit in June, 1941, was 15 years. The mean gain in weight per patient in twenty-four months was 13.9 pounds, or 7 pounds per year. There were three attacks of acute rheumatic fever (25 per cent) and one attack of scarlet fever. Almost all of the children were in a mediocre state of health and had a long list of complaints. They reported an average of three colds for the same period, which is not high, but almost double that of the treated group. Of the twelve, one complained of chronic abdominal pains; two, of frequent nosebleeds; four, of chronic joint and muscle pains; four, of cardiac symptoms; and three, of chronic headaches. Only one said unequivocally that she had no complaints, whereas in the group of formerly treated patients eleven claimed a state of "perfect health" for the previous two years.

Modified Form of Immunization.—Our 101 rheumatic cardiac patients who were treated in the course of the past eight years appear to have derived considerable benefit from active immunization with the hemolytic streptococcus toxin, as present and past records show, but we have been

acutely aware of the cumbersomeness of this form of treatment. It was a burden on the patient, who was required to pay about thirty-eight visits in two years to the clinic, and on the physicians who had to limit themselves to the care of a small group of treated, control, and follow-up patients because of their frequent visits. For a long time we were casting about for a modified form of N. Y. 5 strain which would retain the virtues of crude toxin in protecting the patients against recurrences of acute rheumatic fever, yet would shorten the period of immunization without producing a general or even a severe local reaction. The New York Board of Health informed us that, so far, the hemolytic streptococcus has not lent itself to the production of a toxoid but recommended that we turn to Milton V. Veldee, surgeon of the U. S. Public Health Service, who successfully used a tannic acid precipitated toxin of the N. Y. 5 strain of hemolytic streptococcus in immunizing several thousand public school children against scarlet fever. Since Veldee[4] used the same strain as was used by us, we decided to try his modified toxin with a new group of patients. We estimated that we had been giving to each of our patients, in the course of two years, 35,000 skin-test doses hypodermically of the crude toxin of N. Y. 5 streptococcus. It appeared reasonable to give the same amount of modified toxin of N. Y. 5 in four intradermal inoculations three weeks apart, and to repeat the third dose every six months. The modified toxin was graduated as follows: 5,000, 8,000, 10,000, and 12,000 skin-test doses.

In September, 1940, we started to inoculate forty-two new rheumatic cardiac patients at the New York Post-Graduate Hospital, and, in January, 1941, twenty-nine more patients at the City Hospital by this "short method." The patients and their relatives were pleased by the prospect of a brief course of treatment. We followed Veldee's practice of giving the intradermal inoculations of 0.1 c.c. into the triceps surface of the arm, where the puncture is covered by a sleeve, and the usually mild local reaction does not attract the attention of the patient and others.

This is a preliminary report covering nine months of observation of forty-two patients at the Cardiac Research Clinic at the New York Post-Graduate Hospital. We mention only briefly the group of twenty-nine patients at the City Hospital, for we feel they have not been observed long enough to justify a detailed report.

The 1940 to 1941 control group served for comparison with this new group of patients at the New York Post-Graduate Hospital. Sixteen of the new patients who received the modified treatment belonged to the control group in 1939 to 1940 and have been placed in the "short treatment" group either because they asked for it, or because they were so ill that we wished especially to include them in the group.

TABLE VI

COMPARISON BETWEEN PATIENTS RECEIVING THE MODIFIED TREATMENT AND CONTROL PATIENTS

	TREATED		CONTROL	
No. of patients	42		33	
Sex	27 males; 15 females		17 males; 16 females	
Av. age (yr.)	10.9		12.1	
No. of reported colds per child	1.45		2.9	
Mean gain in weight (lb.)	7.5		7.9	
Abdominal symptoms				
+	8		4	
++	5		4	
+++	2		5	
Pallor				
+	2		3	
++	5		1	
+++	4		12	
Epistaxis				
+	3		3	
++	1		4	
+++	3		0	
Rheumatic pains				
+	9		3	
++	4		3	
+++	3		14	
Cardiac symptoms				
+	5		5	
++	1		1	
+++	3		10	
Headaches				
+	11		1	
++	4		1	
+++	3		11	
Twitching				
+	3		2	
++	2		2	
+++	3		4	
No. of attacks of rheumatic fever, carditis, and chorea	0		11, or 33%	
Deaths	0		3	
Mean laboratory data:				
E.S.R. (mm. per hr.)	9		17	
Hemoglobin (%)	76.1		73.2	
Nonfilamented neutrophiles (%)	8.33		10.5	
Platelets per cu. mm.	210,000		192,000	
Estimation of patient's condition:	*Fall (1940)*	*Spring (1941)*	*Fall (1940)*	*Spring (1941)*
Excellent	5	20	10	8
Very good	8	9	4	2
Good	7	7	5	4
Av.	10	3	5	4
Fair	5	1	5	4
Poor	7	2	4	11

Symbols: +, occurred once; ++, occurred twice; +++, occurred more than twice.

Of the forty-two patients, fifteen were girls and twenty-seven boys. Their average age was the lowest among all the groups, namely, 10.9 years. The number of reported colds per child was also the lowest, viz., 1.45. The mean gain in weight per child was 7.5 pounds in nine months. There were few subacute rheumatic symptoms. Two patients complained of frequent abdominal distress; three, of rheumatic pains on more than two occasions; three, of frequent headaches; and three, of twitching. Not a single patient developed a fresh attack of rheumatic fever, but one who has both congenital and rheumatic heart disease and is chronically decompensated, and another who, at the outset, had moderate chorea, showed no improvement. The blood picture was normal. A glance at Table VI will show the contrast between this group and the thirty-three control children.

These results appear to us by far the most encouraging, especially because we went to great pains in September, 1940, to get a group of children who were the most ill during the preceding winter and especially during spring. The control group of thirty-three patients in September, 1940, contained only five severe cardiac patients, whereas the newly treated group contained thirteen. In the control group, thirteen instances of acute rheumatic fever occurred, with three deaths, but, as stated, in the treated group not a single new attack developed, although two patients showed no improvement.

Twenty-nine patients have been treated by the same method at the City Hospital pediatric clinic since the beginning of 1941. Of those, thirteen were boys and sixteen girls. The average age was 11.5 years. Their mean gain in weight was 3.1 pounds for six months, which would be modest enough if one did not take into account that the patients at the City Hospital come from among New York's poorest. However, only one child developed an attack of chorea. The rest remained well and had few minor complaints, and their sedimentation rates and blood cell counts were normal.

COMMENT

Twice before, we have recorded the satisfactory results of immunization of ambulatory patients suffering from rheumatic heart disease. Sixty-six carefully controlled patients received graduated injections of hemolytic streptococcus filtrate prior to 1939. This paper discusses the condition of thirty-five more rheumatic cardiac children who have received a two-year course of treatment since then. After eight years of trial of this method, we feel that it is fair to say that the treated patients have shown a striking reduction in the number of attacks of acute rheumatic fever, and a marked general improvement in health. Many formerly treated patients have been observed for as long as six

years since the injections were discontinued, and their health has remained materially better than that of untreated patients. If a hemolytic streptococcus toxin has been able to confer immunity upon them, that immunity is of long duration. Our bacteriologic studies show that treated patients would get upper respiratory infections, but they would be of short duration and seldom would be followed by a flare-up of rheumatic fever.

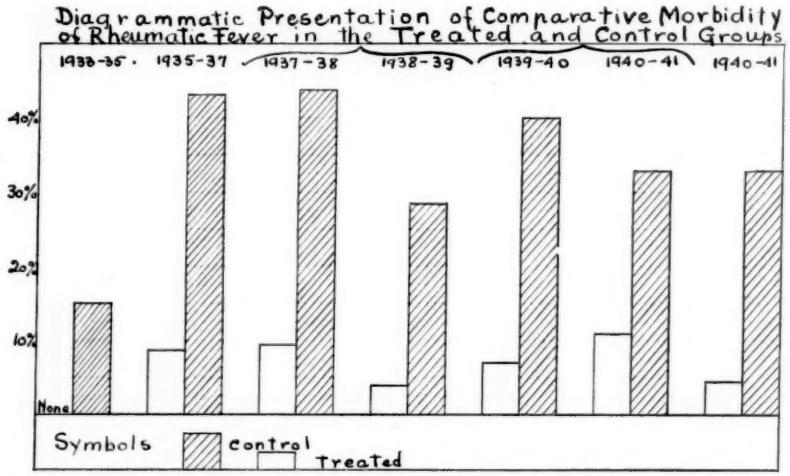

Fig. 1.

However, the drawbacks of this form of protracted prophylactic treatment are obvious, and we have tried an abbreviated method of immunization on forty-two children, giving them the total number of skin-test doses in four (instead of thirty-eight) inoculations intradermally, three weeks apart. The N. Y. 5 toxin has been attenuated with tannic acid, and the intradermal route allows a slow absorption of the toxin. Reactions have been only local, but in a number of highly sensitized children they were as large as 5 to 7 cm. in diameter. The only subjective symptom was itching twenty-four hours later. A number, but unfortunately not all, of the patients received preliminary skin tests for determining sensitivity with one, two, and five skin-test doses of highly purified *Streptococcus hemolyticus* toxin and were retested a month after the fourth inoculation. However, the entire group was skin-tested after the treatment. We shall report on the skin test in another year and hope by that time to treble the number of patients who will have received this abbreviated form of immunization. Almost everyone in this group received the first semiannual inoculation in May or June, 1941. Only prolonged observation will show whether the results of this form of treatment are as lasting as those of the protracted treatment.

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THE INDUCED ANOXEMIA TEST

A Study by Age Groups

Clough Turrill Burnett, M.D., Marshall Grant Nims, M.D., and C. J. Josephson, M.D., Denver, Colo.

ANOXEMIA as a result of some derangement of the gaseous interchange mechanism or a natural diminution of available atmospheric oxygen, as at high altitudes, has attracted an increasing amount of attention in recent years. Among the earliest observations of altitude effects were those of the Pikes Peak Expedition of 1911, when Schneider, Henderson, Haldane, and Douglas spent several weeks at the summit of this 14,110-foot mountain. These men were already well-trained physiologists; they were well equipped; and their observations remain the foundation for all subsequent investigation on the effects of anoxemia.

Although Paul Bert had, some forty years before, called attention to compensatory changes which occur in the blood as a result of residence at a high altitude, it remained for these observers to furnish more accurate data concerning blood changes at high altitudes, as compared to sea level, in the same person, as well as changes in the oxygen carrying capacity of the blood and in the respiratory mechanism, and changes (of especial importance in relation to the subject of this paper) in the circulatory apparatus. Later these and other investigators compared their observations with those obtained by placing a person in a chamber in which the amount or percentage of oxygen could be controlled (low pressure chamber), under conditions simulating those encountered at altitudes ranging from sea level to 22,000 ft. Somewhat later there was introduced a rebreathing apparatus by means of which the subject breathes the air from a tank, thereby causing a progressive decrease of oxygen. Since the carbon dioxide of the expired air is removed by an absorbent, it was thought to be eliminated as a factor in the test, but there appears to be some uncertainty regarding this point.

The results of these various investigations showed that, regardless of the method employed, the effects of low oxygen tension are the same whether they are induced by altitude or dilution, either immediate or slowly induced, and that barometric pressure, per se, is not the cause of these changes, but that such changes are due to variations in the oxygen tension, and that, even at such altitudes as that of the summit of Pikes Peak, all evidence of altitude effects can be eliminated by the

From the Department of Medicine, Colorado University School of Medicine.
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administration of an amount of oxygen sufficient to simulate sea level conditions. This work early attracted the attention of those who were especially interested in the effects of extremely rapid and often repeated changes in altitude, such as are encountered in aviation. Credit should be given to members of our air service for numerous and valuable contributions.

We have thus far mentioned only the application of these studies to normal men, namely, the effects of variously induced anoxemia states. About fifteen years ago (1925 and 1926), reports of the effects of anoxemia on the heart began to appear in medical literature. It was pointed out by Resnik[1] that, under conditions of anoxemia, changes in cardiac impulse conduction occur and that a damaged heart, when subjected to anoxemia, may early exhibit functional disturbances which will appear only in the presence of a more profound anoxemia in the normal heart.

The theory advanced by Danielopolu,[2] namely, that angina pectoris is due to a disproportion between the flow of blood in the coronary vessels, on the one hand, and the work of the heart, on the other, furnishes a basis for the test under consideration. He pointed out that, even if a heart has normal arteries, and the demands are great enough, coronary artery insufficiency may become so marked as to lead to angina, and that, when these arteries are diseased, lesser demands will bring on the anginal syndrome. The author presented this explanation of angina but did not offer satisfactory evidence that there may be coronary insufficiency in the presence of normal coronary arteries. This evidence appeared much later in the work of Rothschild and Kissin,[3] Levy, et al.,[4] and others.

At about this time (1928), Keefer and Resnik[5] expressed the belief that angina pectoris is always due to anoxemia of the myocardium and that there is a great difference in the response of different hearts to anoxemia, which is dependent upon varying ability to compensate, and that infarction depends upon the rapidity of occlusion and the richness of the previously existing anastomoses; both factors determine the degree of local anoxemia attained.

In the past decade, numerous workers have presented evidence of changes in the electrocardiogram as a result of myocardial ischemia induced by ligation of coronary arteries,[6-8, 39] by the local effect of vasoconstrictors,[7] and, finally, by brief attacks of angina pectoris.[9, 10] In each instance, the changes which occur are in many respects comparable to those which follow occlusion of one of the coronary arteries, namely, alterations in the amplitude or direction of the T waves and shifts in the position and form of the S-T segments. Experimental proof[10] was presented that myocardial ischemia is responsible for these changes, and that this localized ischemia is due to coronary artery insufficiency, which is either functional (due to an excessive demand for

blood flow) or organic (due to some form of narrowing of the coronary vessels). Parallel clinical observations[11] demonstrated, in addition to the above-mentioned electrocardiographic changes in response to anoxemia induced by various means, that it is also "possible to reproduce the pain of angina pectoris in susceptible subjects" and that the coronary circulation, which is normally adequate, becomes inadequate during anoxemia. Pain in other muscles under anoxic conditions was studied. It was demonstrated[12] that exercise of the forearm under anoxic conditions will induce pain which disappears when the blood is flushed with oxygen and that no pain occurs if the oxygen supply is adequate. The suggestion was advanced that the pain of angina may be due to the muscular activity of the heart in the presence of oxygen deficiency. In a recent study,[13] after ligation of a coronary artery and recovery therefrom, animals were subjected to induced anoxemia. An increase in the RS-T deviation which was already present as a result of the ligation was observed in twelve of fourteen animals; this seemed to justify the use of the test in the differential diagnosis of coronary insufficiency.

In summary, it has been shown that attacks of anginal pain induced by anoxemia are identical with spontaneous attacks, that anoxemia is at least in part responsible for the pain of angina pectoris, and that, associated with either spontaneous or induced attacks, there are characteristic changes in the electrocardiogram.[4, 9, 10, 14] Finally, it has been suggested that these responses to induced anoxemia can be employed in the diagnosis of impairment of the coronary circulation.[4]

In February, 1939, Levy, Bruenn, and Russell[4] presented a clinical test for coronary insufficiency which was based upon the foregoing evidence. In a subsequent paper, Levy and his associates modified their criteria somewhat, but, in the main, substantiated their earlier report. Some of their critics, including the senior author, entertained some hesitancy regarding the acceptance of their criteria, for it appeared that (1) these criteria had been based upon an insufficient number of normal subjects, and (2) there was nothing in the report of these observers to indicate that they had made a comparative study of the response to induced anoxemia at various ages. It seemed rather probable that persons of widely varying ages might not respond similarly to a given stress; that is, that the normal response at fifty years, and above, would probably differ from that observed in young persons. With this in mind, apparently, May[35] studied the effect of anoxemia in a group of fifty normal persons and twenty patients with various types of heart disease. He used the rebreathing method, the results of which we believe are not quite comparable to those obtained with the dilution method previously employed by Levy, and later by Levy and ourselves, in which the expired carbon dioxide is passed out immediately, thus preventing any side effects of carbon dioxide, and, at the same time, ensuring a constant percentage of oxygen, regardless of the duration

of the test. In the rebreathing method employed by May, the subject depletes the oxygen in the air until it reaches the point of anoxemia. In our method the subject has his full oxygen reserve at the beginning of the test; in the rebreathing method the oxygen reserve is steadily depleted. In rebreathing it appears impossible to know the point at which the loss of reserve passes over into the anoxemic state, and it is therefore impossible to ascertain the time element with any degree of accuracy. The duration of May's tests ranged from seven to fourteen minutes and electrocardiograms were taken before, during, and at approximately three minutes after the test. It would seem that some of his records may have been taken before anoxemia developed. In rebreathing, anoxemia is brought about by metabolic utilization of oxygen, the rate of which varies with the weight, degree of mental excitement, and age of the subject. It also varies according to the length of period of rest and whether or not food has been taken. It is not possible, therefore, for May to state from his work the degree of anoxemic stress to which the subject was exposed, but it is reasonable to assume that, because of the higher average metabolic rate in the young, the anoxemic stress in this group was greater. We believe his observation that "the effect of oxygen deficiency, as measured by diminution in the height of the T waves, lessens considerably with advancing age" is unwarranted in view of the above-mentioned considerations. We feel, therefore, that May's comparison of the responses to anoxemia at various ages is not valid. Because of these apparent inaccuracies in the rebreathing method, we instituted in the summer of 1939 a study of the clinical and electrocardiographic response to induced anoxemia, employing the dilution method previously described by Levy, et al.[4]

TABLE I

OXYGEN PERCENTAGES EMPLOYED, WITH ALTITUDE EQUIVALENTS[50]

10% oxygen at sea level	=		altitude 20,800 ft.
10% oxygen at 5,420 ft. (Denver)	= 8.29% at sea level	=	altitude 25,900 ft.
12% oxygen at 5,420 ft. (Denver)	= 9.95% at sea level	=	altitude 20,200 ft.
8.6% oxygen at 5,420 ft. (Denver)	= 7.13% at sea level	=	altitude 31,000 ft.*

*The altitude equivalent for 8.6 per cent oxygen can only be approximated as the FitzGerald Chart No. 2 (p. 253) employed does not permit direct reading of the altitude, that is, a curved line must be extended and estimation made therefrom.

The gas mixture in our tanks approximated 10 per cent oxygen and 90 per cent nitrogen, except in the study of two small groups which are presented separately, in which the percentages of oxygen were 12 and, by error, 8.5, respectively. Actually, these are equivalent to sea level, as shown in Table I. The approximate altitude represented by these percentages is also shown.

These percentage figures are derived by use of the following formula:

$$\frac{\times \text{ (sea level equivalent)}}{630} = \frac{\%\text{ oxygen in tank}}{760}$$

Average barometric pressure at sea level, 760; average barometric pressure at Denver, 630.

10% oxygen	$\frac{\times}{630} = \frac{0.10}{760}$	$\times = 8.29\%$
12% oxygen	$\frac{\times}{630} = \frac{0.12}{760}$	$\times = 9.95\%$
8.6% oxygen	$\frac{\times}{630} = \frac{0.086}{760}$	$\times = 7.13\%$

Most of the observations relative to the effect of induced anoxemia reported by Levy and others were made under anoxemia produced by 10 per cent oxygen mixtures. It is well recognized that residence at an altitude no higher than that of Denver confers some adaptation to the diminished oxygen content of the air. This varies with the person, but we feel that it is probably sufficient to compensate for the difference in oxygen percentage observed when the gas is passed from the pressure tank into a rubber bag, and thus exposed to the low partial pressure of this altitude. Therefore, since we wished to make comparable observations, although we recognize this difference in partial pressure between sea level and Denver, we have employed mainly a 10 per cent oxygen mixture. *Throughout this paper we shall state the percentage of oxygen existing in the tanks, rather than that in the bag immediately before inhalation.*

In the early stage of this investigation we encountered some difficulty in obtaining a dependable and fairly constant oxygen-nitrogen mixture. We learned that a gas analysis of each tank was required because a permissible error of 1 per cent in the oxygen percentage (our standard) might be exceeded by the manufacturers. Our experience teaches that a producer's guarantee should always be supplemented by a gas analysis.

As stated previously, we felt that a comparison of the response to anoxemia at various ages might show a sufficient difference to be of clinical importance; that is, we suspected that the response of the normal person in the "coronary" age might differ perceptibly from that of the man in the third and fourth decades. Since no published studies, save those of May, which have already been discussed, indicated that such a comparison had been made, we proceeded to select subjects for this test in groups according to age by decades.

SELECTION OF CASES

For the most part, the patients, particularly those 41 to 50 and 51 to 60 years old, were selected from the outpatient medical service; those who were 21 to 30 and 31 to 40 were mainly medical students and nurses. All subjects were free of any cardiovascular symptoms or signs, pulmonary symptoms, and abnormal electrocardiographic changes.

PROCEDURE

In each instance the subject rested in bed for one hour prior to the start of the test to insure near-basal conditions. With the apparatus in place beside the bed, the purpose of the test was re-explained, together with some of the symptoms which might ensue, that is, numbness and tingling of the extremities, palpitation, precordial pain, and "lightness in the head." The subject was cautioned that any severe pain which developed should be localized with the right hand; any "short-windedness" or "feeling as of running" could best be minimized by breathing more rapidly or more deeply, but at all times *regularly*. It was emphasized that the "air mixture" bag (10 per cent oxygen and 90 per cent nitrogen) would always be full and the supply ample. The more slowly and simply these details were explained to each subject, the less apprehensive and more confident he became, and discontinuation of the test because of discomfort or "nervousness" was minimized.

The well-moistened mouthpiece was then adjusted comfortably between the lips and teeth, and the nose clip was attached; both were tested to insure a "closed system." A control electrocardiogram was then taken, after which the subject was given the gas mixture from the inflated bag instead of room air.

The blood pressure, pulse rate, and electrocardiogram were recorded every five minutes. At the end of twenty minutes, 100 per cent oxygen was given for one minute, after which the blood pressure, pulse rate, and electrocardiogram were again recorded. The apparatus was then removed, and the blood pressure, pulse rate, and electrocardiogram were obtained at five- and ten-minute intervals. Throughout the test the lips and mouthpiece were kept moist to insure the maintenance of a "closed system." At two- to three-minute intervals the patient was tested for response to auditory and visual stimuli, and these were recorded; the latter consisted of a request to look at the observer's forehead, and the promptness of response, as well as power of concentration, was recorded in terms of "good," "poor," or "no response." At varying intervals the subject was reassured that the test was proceeding satisfactorily.

If the subject developed severe precordial pain, undue restlessness, clonic muscle contractions, or unresponsiveness to auditory or visual stimuli at any time during the test, 100 per cent oxygen was given for one minute, the blood pressure and pulse rate were recorded, and an electrocardiogram was taken. Following this, while the subject was breathing room air, the electrocardiogram, blood pressure, and pulse rate were recorded at two succeeding five-minute intervals.

CHANGES IN THE ELECTROCARDIOGRAM OF THE NORMAL SUBJECT CAUSED BY BREATHING A MIXTURE OF 10 PER CENT OXYGEN AND 90 PER CENT NITROGEN

The changes in the first age group (21 to 30 years) are graphically shown in Fig. 1, which represents the average of the exact measurements of the height or depression of the RS-T segment and the T waves. In this series there were fifty normal subjects. For the reader who is interested in greater detail than can be shown in graphic form we present Tables II and III, which give the average measurements. A study of Fig. 1 and Tables II and III shows that in the normal subject there is an early and prompt depression of all T waves, particularly T_3, which regularly becomes flat or nearly so, and that with this change there is a deviation of the RS-T segment from the isoelectric line; both

changes reach their maximum at the end of the twenty-minute exposure to the 10 per cent oxygen mixture.

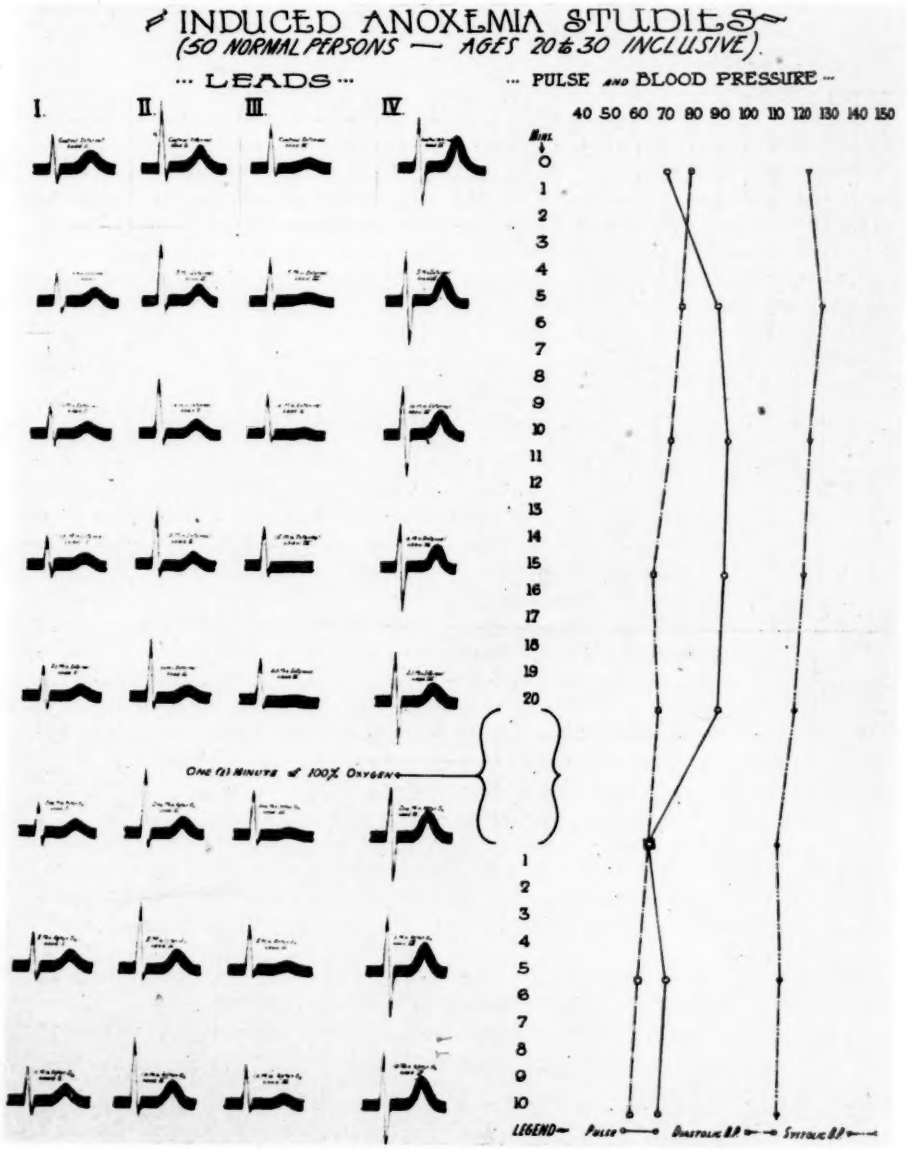
INDUCED ANOXEMIA STUDIES
(50 NORMAL PERSONS — AGES 20 & 30 INCLUSIVE).
LEADS
I.
II.
III.
IV.
PULSE AND BLOOD PRESSURE
40 50 60 70 80 90 100 110 120 130 140 150
MIN.
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
ONE (1) MINUTE @ 100% OXYGEN
1 2 3 4 5 6 7 8 9 10
LEGEND — PULSE — DIASTOLIC B.P. — SYSTOLIC B.P.

Fig. 1.

In our control electrocardiograms, taken before the administration of the 10 per cent oxygen mixture, we encountered slight left axis deviation in about the same frequency in all age groups. In all instances in which this occurred it was consistent with the habitus of the subject, and, since we find that anoxemia causes no consistent or

TABLE II

THE RS-T INTERVAL

AGE (YR.)	DATA	CONTROL	MINUTES OF 10% O_2 90% N				MINUTES AFTER 100% O_2		
			5 MIN.	10 MIN.	15 MIN.	20 MIN.	1 MIN.	5 MIN.	10 MIN.
					Lead I				
21 to 30	Max.	+1.0	+1.0	+0.5	+0.5	0.0	0.0	0.0	0.0
	Av.	+0.1	0.0	0.0	0.0	−0.1	0.0	0.0	0.0
	Min.	0.0	0.0	−0.5	−0.5	−1.0	−0.5	0.0	0.0
31 to 40	Max.	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Av.	0.0	0.0	0.0	−0.1	0.0	0.0	0.0	0.0
	Min.	0.0	0.0	−0.5	−1.0	−0.5	0.0	0.0	0.0
41 to 50	Av.	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
51 to 60	Max.				0.0	0.0	0.0		
	Av.	0.0	0.0	0.0	−0.1	−0.1	−0.1	0.0	0.0
	Min.				−1.0	−1.0	−1.0		
					Lead II				
21 to 30	Max.	+2.0	+2.0	+1.0	+1.0	+1.0	+0.5	+1.0	+1.0
	Av.	+0.2	+0.1	+0.0	−0.1	−0.2	−0.0	+0.1	+0.1
	Min.	−0.5	−1.0	−1.0	−1.0	−2.0	−0.5	0.0	0.0
31 to 40	Max.	+1.0	+0.5	+0.5	0.0	0.0	0.0	0.0	+0.5
	Av.	+0.1	0.0	−0.1	−0.3	−0.5	−0.1	0.0	0.0
	Min.	0.0	−1.0	−1.0	−2.0	−1.0	−1.0	0.0	−0.5
41 to 50	Max.	+1.0	+0.5	0.0	0.0	0.0	0.0	0.0	+1.0
	Av.	+0.1	−0.1	−0.2	−0.6	−0.4	0.0	0.0	0.0
	Min.	−0.5	−1.0	−1.0	−2.0	−1.5	−1.0	−0.5	0.0
51 to 60	Max.	+1.0	+1.0	+1.0	0.0	+0.5	+1.0	+0.5	+0.5
	Av.	0.0	0.0	−0.1	−0.2	−0.3	0.0	0.0	0.0
	Min.	−0.5	−1.0	−1.5	−1.0	−1.0	−0.5	−0.5	0.0
					Lead III				
21 to 30	Max.	+0.5	+0.5	+1.0	+0.5	+0.5	+0.5	+0.5	+1.0
	Av.	+0.1	+0.1	0.0	−0.2	−0.3	0.0	0.0	0.0
	Min.	−0.5	−0.5	−1.0	−1.0	−1.0	−0.5	−0.5	0.0
31 to 40	Max.	+0.5	+0.5	0.0	0.0	0.0	+0.5		
	Av.	0.0	0.0	−0.1	−0.2	−0.3	0.0	0.0	0.0
	Min.	−0.5	−0.5	−1.0	−1.0	−1.5	−1.0		
41 to 50	Max.	+0.5	0.0	0.0	0.0	0.0	0.0		
	Av.	0.0	0.0	−0.1	−0.1	−0.1	0.0	0.0	0.0
	Min.	0.0	−1.0	−1.0	−2.0	−1.0	−0.5		
51 to 60	Max.	+0.5	+0.5	+0.5	0.0	+0.5	+0.5	+0.5	+0.5
	Av.	+0.2	0.0	−0.1	−0.1	−0.2	0.0	0.0	0.0
	Min.	−0.5	−1.0	−1.0	−1.0	−1.0	−0.5	−0.5	0.0
					Lead IV				
21 to 30	Max.	+2.0	+1.5	+2.0	+1.5	+2.0	+1.0	+1.0	+2.0
	Av.	+0.2	+0.1	−0.1	−0.1	0.0	+0.1	+0.1	+0.1
	Min.	0.0	0.0	−1.0	−1.0	−3.0	0.0	0.0	0.0
31 to 40	Max.	+2.0	+1.0	0.0	+1.0	+0.5	+1.0	+1.0	+1.0
	Av.	+0.2	+0.1	0.0	0.0	0.0	+0.1	+0.1	+0.1
	Min.	0.0	0.0	−0.5	−1.0	−0.5	0.0	0.0	0.0
41 to 50	Max.	+1.0	+1.0	+1.0	+1.0	+1.0	+1.0	+1.0	+1.0
	Av.	0.0	0.0	0.0	0.0	−0.5	0.0	0.0	0.0
	Min.	0.0	−0.5	−1.0	−1.0	−1.0	−0.5	0.0	0.0
51 to 60	Max.	+1.0	+1.0	+1.0	+1.0	+1.0	+1.0		
	Av.	+0.1	+0.1	0.0	0.0	−0.1	0.0	0.0	0.0
	Min.	0.0	0.0	−0.5	−1.0	−1.5	−0.5		

TABLE III

THE T WAVE

AGE (YR.)	DATA	CONTROL	MINUTES OF 10% O_2 90% N				MINUTES AFTER 100% O_2		
			5 MIN.	10 MIN.	15 MIN.	20 MIN.	1 MIN.	5 MIN.	10 MIN.
					Lead I				
21 to 30	Max.	+5.0	+4.0	+3.5	+3.5	+3.0	+4.5	+4.0	+5.0
	Av.	+2.5	+1.7	+1.4	+1.2	+1.2	+1.6	+2.3	+2.4
	Min.	+1.0	+0.5	−0.5	−0.5	−0.5	0.0	+1.0	+1.0
31 to 40	Max.	+5.0	+2.0	+2.5	+3.0	+2.0	+4.0	+5.0	+6.0
	Av.	+2.2	+1.4	+0.9	+0.8	+0.6	+1.4	+1.9	+2.0
	Min.	+1.0	+0.5	−0.5	−1.5	−1.0	0.0	+0.5	+1.5
41 to 50	Max.	+3.0	+2.0	+2.0	+1.0	+1.0	+3.0	+3.0	+4.0
	Av.	+1.5	+1.0	+1.0	+0.5	+0.2	+1.2	+1.5	+1.6
	Min.	+0.5	0.0	0.0	−1.0	−2.0	−0.5	+0.5	+0.5
51 to 60	Max.	+4.5	+3.0	+3.0	+3.0	+3.0	+3.0	+4.0	+4.0
	Av.	+2.0	+1.2	+1.0	+0.4	+0.7	+1.1	+2.2	+2.1
	Min.	+0.5	0.0	−0.5	−1.0	−1.5	−1.0	+0.5	+0.5
					Lead II				
21 to 30	Max.	+8.5	+6.0	+4.5	+4.5	+5.0	+6.0	+6.0	+6.0
	Av.	+3.3	+2.1	+1.7	+1.5	+1.2	+2.2	+2.9	+3.2
	Min.	+0.5	−1.5	−2.0	−3.5	−3.0	−1.5	+1.0	+1.0
31 to 40	Max.	+5.0	+2.0	+3.0	+2.0	+4.0	+4.0	+4.5	+5.0
	Av.	+3.1	+1.7	+1.1	+1.0	+0.9	+1.8	+2.6	+2.8
	Min.	+2.0	+0.5	−2.0	−2.0	−2.5	−2.0	+1.0	+2.0
41 to 50	Max.	+6.0	+4.0	+3.0	+3.0	+2.5	+5.0	+5.0	+5.0
	Av.	+3.2	+1.6	+1.3	+1.3	+1.3	+2.2	+3.0	+3.0
	Min.	+1.0	−0.5	−2.0	−3.0	−3.0	−1.5	+1.0	+2.0
51 to 60	Max.	+5.5	+4.5	+4.0	+4.0	+3.5	+6.0	+5.0	+7.0
	Av.	+3.2	+2.2	+1.9	+1.7	+1.7	+2.6	+2.9	+3.1
	Min.	+0.5	−1.0	−1.0	−1.0	−1.0	−1.0	−1.5	−1.0
					Lead III				
21 to 30	Max.	+4.0	+4.0	+2.5	+2.5	+2.5	+3.5	+4.0	+4.0
	Av.	+1.0	+0.7	+0.2	−0.2	−0.2	+0.5	+0.9	+1.0
	Min.	−2.0	−2.0	−2.0	−3.0	−3.0	−2.0	−1.5	−1.0
31 to 40	Max.	+2.0	+2.0	+2.0	+2.0	+3.0	+2.0	+2.0	+3.0
	Av.	+0.9	+0.2	0.0	0.0	0.0	+0.4	+0.8	+1.8
	Min.	−1.5	−2.0	−3.0	−3.0	−2.5	−1.5	−2.0	−2.0
41 to 50	Max.	+4.0	+3.0	+2.0	+2.0	+2.0	+3.0	+3.0	+4.0
	Av.	+1.6	+0.9	+0.2	+0.2	+0.2	+1.0	+1.4	+1.6
	Min.	−1.0	−1.0	−1.0	−2.0	−1.5	−1.0	0.0	0.0
51 to 60	Max.	+6.0	+3.0	+5.0	+2.0	+3.5	+3.0	+3.5	+3.0
	Av.	+1.2	+1.3	+0.8	+0.7	+0.8	+1.2	+1.1	+1.1
	Min.	−1.0	−0.5	−0.5	−1.0	−0.5	−0.5	−1.0	−0.5
					Lead IV				
21 to 30	Max.	+9.0	+10.0	+9.0	+9.0	+6.0	+9.0	+8.0	+11.0
	Av.	+5.0	+4.1	+3.6	+3.1	+2.7	+4.0	+4.6	+4.7
	Min.	+2.0	0.0	−1.0	−2.0	−2.5	−0.5	+1.0	0.0
31 to 40	Max.	+8.0	+7.0	+7.0	+5.0	+6.0	+6.0	+7.5	+8.0
	Av.	+3.5	+2.4	+2.0	+1.6	+1.5	+2.4	+3.1	+3.1
	Min.	+2.0	−0.5	−0.5	−1.0	−2.5	−0.5	+1.0	0.0
41 to 50	Max.	+9.0	+7.0	+6.0	+5.0	+6.0	+8.0	+8.0	+9.0
	Av.	+3.8	+2.1	+1.5	+1.0	+1.0	+2.0	+3.1	+3.5
	Min.	+1.0	−1.5	−3.0	−4.0	−4.5	−1.5	−1.0	0.0
51 to 60	Max.	+13.0	+11.0	+8.0	+8.0	+8.0	+10.0	+10.0	+11.0
	Av.	+5.3	+4.2	+2.8	+2.9	+2.6	+4.0	+4.5	+4.3
	Min.	+2.0	+1.0	−0.5	−1.0	−1.0	+1.0	0.0	0.0

significant changes in the R and S waves, we have considered as of no clinical importance the presence of slight left axis deviation in an otherwise normal person of sthenic habitus. T_4 showed a variable height and was higher in the fifth than the fourth decade; for this we have no explanation. Two subjects not included in our normal series showed T_4 inversion in the control which was suggestive of coronary artery disease. In both, the wave became upright during anoxemia.

According to Levy, in the presence of coronary insufficiency these RS-T segment and T-wave changes become greatly exaggerated. Partial or complete reversal of T waves may occur with or without these RS-T deviations (for details, see Levy's criteria, below). Usually when the 10 per cent oxygen and 90 per cent nitrogen mixture is replaced with pure oxygen for one minute, followed by respiration of air, these changes quickly disappear, and, by the end of the ten minutes, the curve returns to the form of the control record.

Tables II and III present the average measurements of the RS-T segments and the T waves in the four age groups. In the first this represents an average of fifty cases; in the others it is twenty-five cases, for restudy of measurements obtained in the first group indicated that a sample of twenty-five cases was adequate.

In order to establish these averages, all deflections were measured and recorded to the nearest 0.1 mm.

The maximum and minimum deflections of the RS-T segments and T waves are also shown respectively above and below the figure representing the average of these measurements.

Both the maximum and minimum figures represent a single case in the series of fifty between the ages of 21 and 30 years, and in a series of twenty-five each in each succeeding decade.

Since the individual electrocardiogram must be interpreted on the basis of such maximum and minimum deflections, the presentation of this spread appears desirable.

Only a few persons more than 30 years of age were subjected to anoxemia prior to the completion of our first series (aged 21 to 30 years). From these few observations and on the assumption that as age advances there should be some limitation in the coronary bed, we expected to find that the response would differ perceptibly in the older subjects. This was incorrect, for the response in each of the four decades which we studied was practically identical, as shown by a comparison of Figs. 2, 3, and 4 with Fig. 1 and Tables II and III. Although Levy and others had made this assumption in formulating their criteria for the normal response, there has been no previous work on which an authoritative statement could be based. These anoxemia tests extended over a period of nineteen months. Most of the normal subjects of the 51 to 60 year group were subjected to the test eight months after the youngest group, and therefore at a period when we were most familiar with the technique of the procedure. Since the

oldest subjects showed an average response which was practically identical with the average for the youngest, who were studied first, we feel justified in stating that these normal standards are dependable.

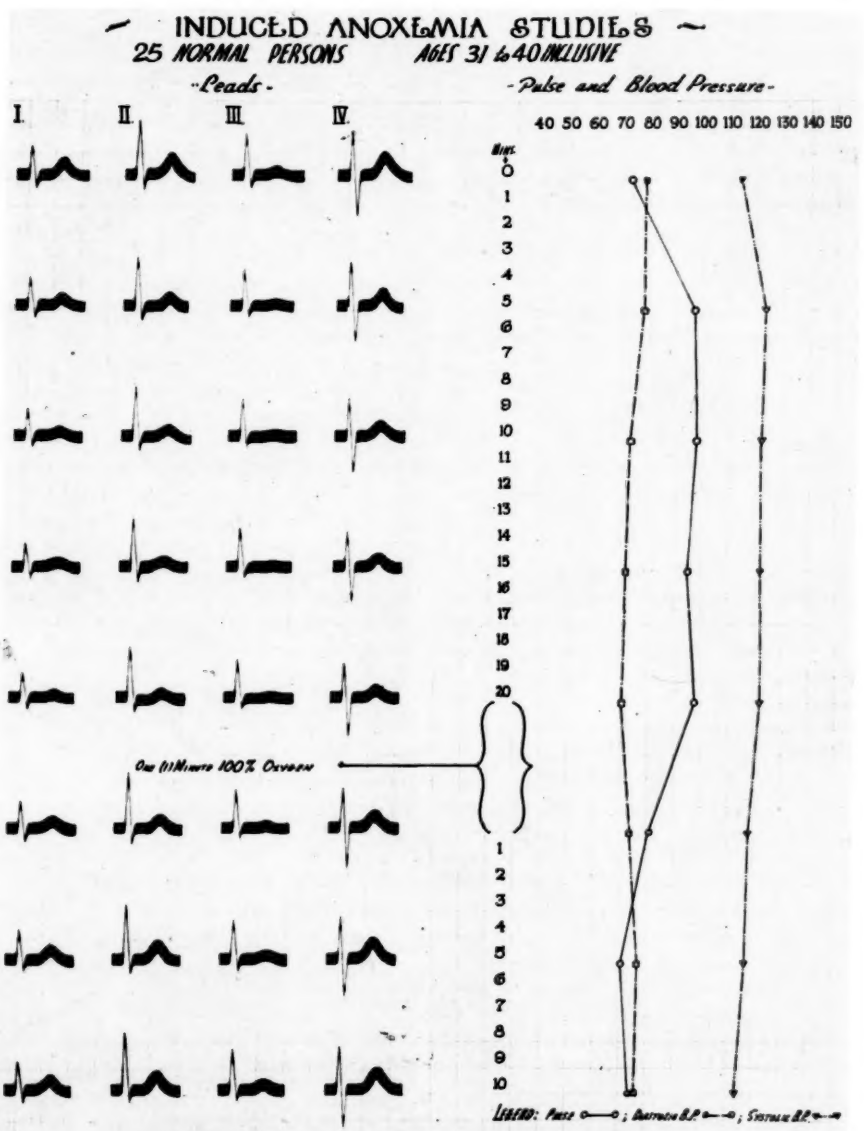

Fig. 2.

As will be shown later, we have encountered numerous difficulties and many causes for error; the latter have been corrected. We have had as critical observers, in addition to our own team of four, two experienced physiologists and one who has, throughout the past thirty years,

been engaged in investigative medicine and is especially occupied with problems of aviation medicine. These men not only observed but submitted themselves to the tests and made valuable suggestions toward improving and safeguarding the procedure.

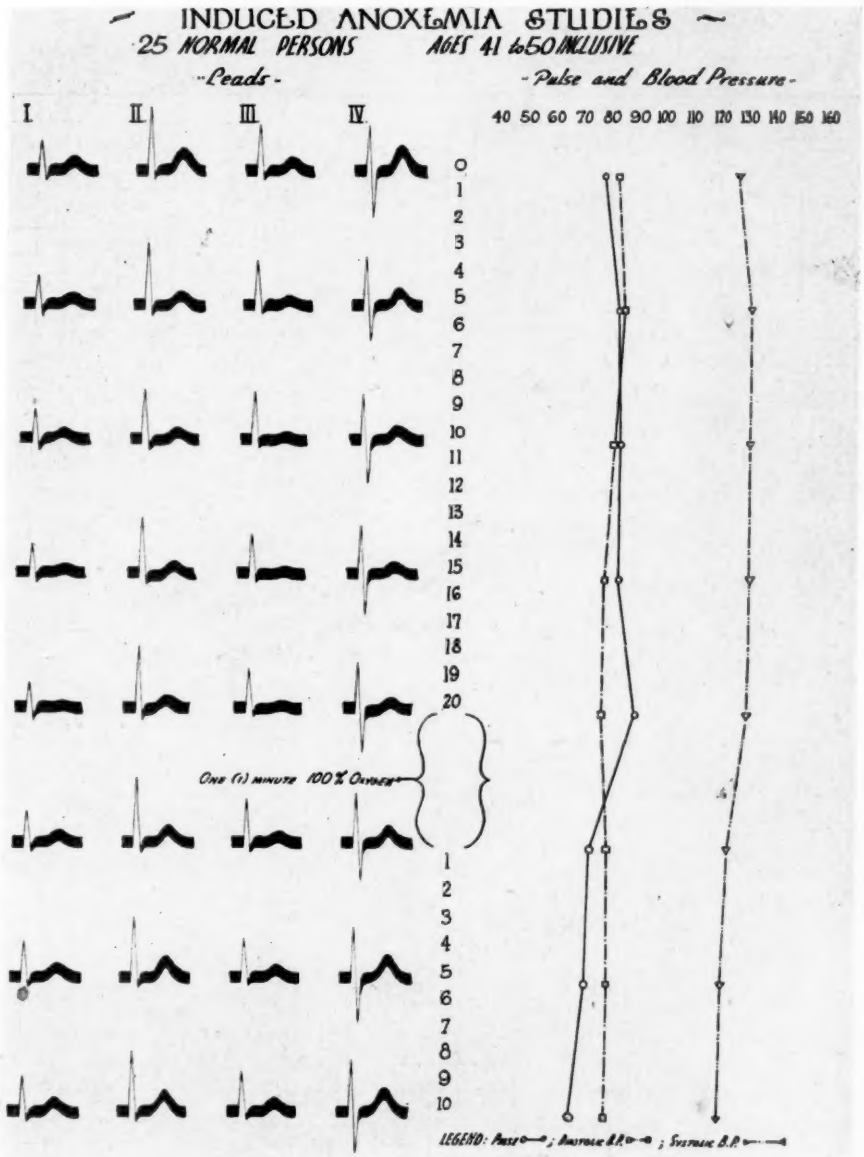

Fig. 3.

The pulse rate and blood pressure responses to anoxemia are shown in Figs. 1 to 4, inclusive. In the younger subjects (21 to 40 years), the

pulse showed a prompt, but moderate, increase in rate as soon as the subject was exposed to the low oxygen mixture. There was no further significant increase. The pulse rate returned to the control level as

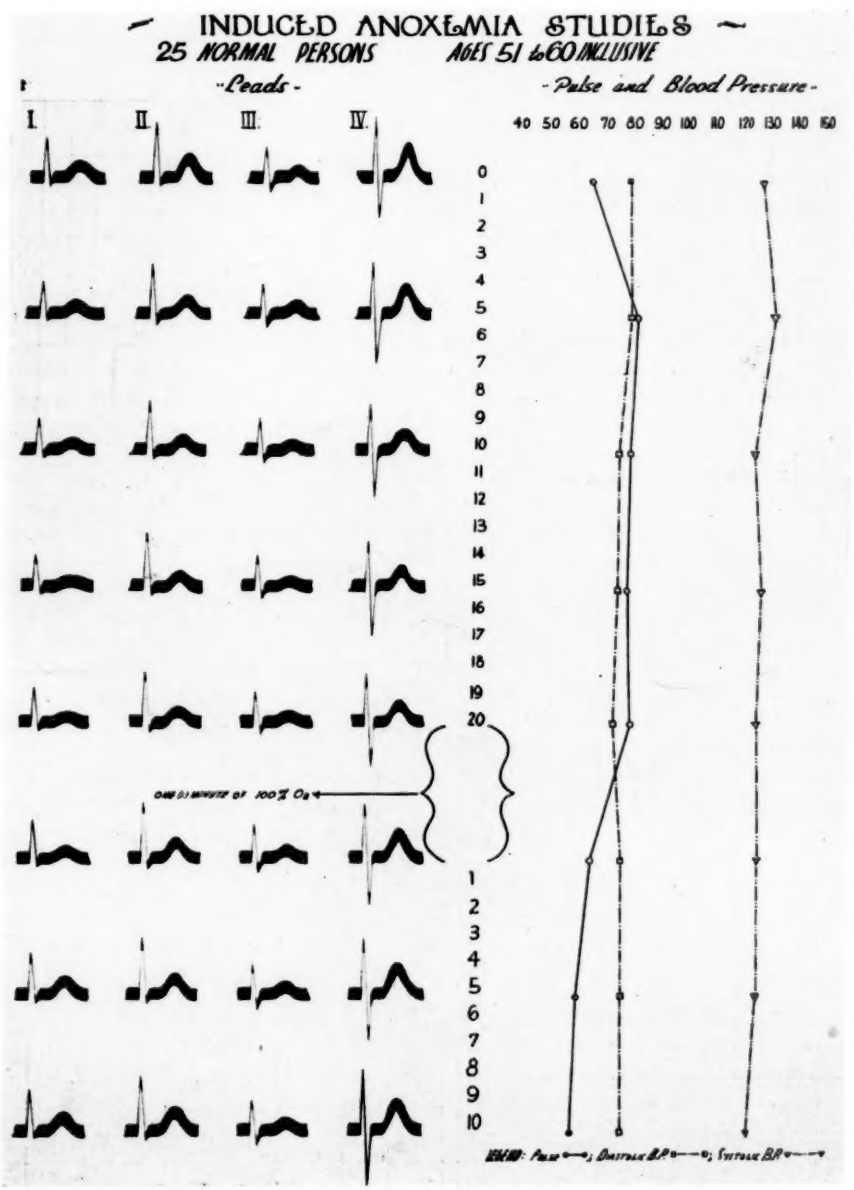
INDUCED ANOXEMIA STUDIES
25 NORMAL PERSONS AGES 51 to 60 INCLUSIVE
-Leads-
-Pulse and Blood Pressure-
I
II
III
IV
40 50 60 70 80 90 100 110 120 130 140 150
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
ONE (1) MINUTE OF 100% O2
1 2 3 4 5 6 7 8 9 10

Fig. 4.

soon as oxygen was inhaled. The changes thereafter were not significant. In the older subjects (41 to 60 years) the pulse rate changes were less marked. In the "normal" subject we did not find significant

blood pressure changes in response to anoxemia. Our observations do not confirm those of Gellhorn[19, 48] and of Steiner, et al.,[49] who report elevation in blood pressure under anoxemia. We do not consider that the pulse rate and blood pressure changes described above have any clinical significance, but marked departure from this range of response may indicate an unfavorable and possibly dangerous reaction.

SUMMARY OF THE ELECTROCARDIOGRAPHIC OBSERVATIONS ON NORMAL SUBJECTS WHO SHOWED A "NORMAL" RESPONSE TO ANOXEMIA

There is an early and prompt depression of all T waves, especially T_3, and, with this, a deviation of the RS-T segment from the isoelectric line; both become maximum at twenty minutes, and both return to the position observed in the control for that subject after the administration of pure oxygen, followed by air (see Tables II and III, and Figs. 1, 2, 3, and 4).

The foregoing is, in all essentials, in agreement with the criteria of Levy, et al.,[4] for the normal response to anoxemia, except the changes in Lead IVF, which will be discussed later.

We wish to present at this point, in summary,* a group of cases in which there was no history or objective evidence of cardiovascular disease, including the control electrocardiogram, but in whom an "abnormal" response, according to the criteria of Levy,[16] was obtained.

LEVY'S CRITERIA OF AN ABNORMAL RESPONSE

1. The arithmetic sum of the RS-T deviations in all four leads (I, II, III, and IVF) totals 3 mm. or more.
2. Partial or complete reversal in the direction of T in Lead I, if accompanied by RS-T deviation of 1 mm. or more in this lead.
3. Complete reversal in the direction of T in Lead IVF, regardless of RS-T deviation.
4. Partial reversal in the direction of T in Lead IVF, if accompanied by RS-T deviation of 1 mm. or more in this lead.

NORMAL SUBJECTS WHO SHOWED AN ABNORMAL RESPONSE TO ANOXEMIA

Some subjects showed what was, according to Levy, an abnormal response to induced anoxemia, but the history, absence of symptoms, and physical examinations failed to reveal any evidence of cardiovascular disease. In none of these was there any history of chest pain, congestive failure, or hypertension. In all cases the control electrocardiogram was normal in all four leads.

Summary.—Twenty-four of 125 normal persons (19.2 per cent) showed an abnormal response according to the criteria of Levy. Twenty-two of the twenty-four subjects showed complete reversal of T in Lead IVF (Levy Criterion 3); two of these also showed total RS-T deviations

*The detailed protocols which were presented to the editor are omitted from this publication. Mimeographed copies of all case protocols will be furnished on request to the senior author.

of 3 mm. or more (Levy Criterion 1); and one showed complete reversal of T_1 with RS-T deviation of 1 mm. (Levy Criterion 2). The age distribution of these is given in Table IV. When reversal of T_4 occurred, it was observed that it was not always consistent. In several of the records it was noted that reversal was greater at fifteen than at twenty minutes.

TABLE IV

TOTAL NO. OF SUBJECTS	AGE (YR.)	SUBJECTS WHO SHOWED ABNORMAL RESPONSE		LEVY CRITERION NO.
		NO.	%	
50	21 to 30	5	10	3
25	31 to 40	6	24	3
25	41 to 50	8	32	3
25	51 to 60	5	20	3

It therefore appears that *reversal of T in Lead IVF (Criterion 3) in response to induced anoxemia cannot be accepted as indicative of coronary insufficiency.*

In two instances the control electrocardiogram suggested coronary disease, but there was no other confirmatory evidence. The response to anoxemia was "normal," according to Levy.

Five subjects were given 12 per cent oxygen and 88 per cent nitrogen at an early stage in this work and were therefore not included. Three of these complained of precordial pain, and we felt that one of them had probably had an old infarction. In the case of the other two we doubted the importance of this complaint. This particular gas mixture was used after one or two rather disquieting experiences, to be mentioned later, with the idea that a lesser degree of anoxemia might prevent undue strain and thus eliminate these effects. We found, however, that there appeared to be no significant difference between the response of these subjects and that of those who received the 10 per cent oxygen mixture, and, since we were attempting to set up normal standards for a clinical test, it seemed preferable to employ the same gas mixture throughout. The results of these tests were quite comparable to those in which the 10 per cent mixture was used, but are not included with them.

We present, in Table V, forty-five anoxemia observations which are not included in the series of 125 normal subjects. These appear in four groups. It will be noted that in twenty-four instances the test was interrupted. Since this usually occurred *after* definite evidence of profound anoxemia, especially in Group II, we believe that the inclusion of these results is warranted. In six instances we considered the results of no value because no significant anoxemic effect was produced. These are reported as "no record," and are included only in order to point out certain causes of failure in the anoxemia test.

There were nine cases in which there was a complaint of precordial pain of some type; in none of these had there ever been any objective evidence of cardiovascular abnormality. Of this group, *only two gave an abnormal response,* according to Levy's criteria, and one conformed

to all of the four criteria indicative of coronary insufficiency, but all other evidence in these cases was against this diagnosis.

In four of fifteen subjects who presented no acceptable evidence of cardiovascular disease, but, because of complaints, history of past disease, or confusing electrocardiograms, were not considered satisfactory for inclusion as normal subjects, we obtained a response which was abnormal, according to Levy. Since this study was primarily an attempt to set up normal standards, we avoided the intentional inclusion of persons who showed acceptable evidence of cardiovascular disease. However, seven persons who presented definite or equivocal evidence of a cardiac abnormality are presented in Group IV. Five of the seven showed an abnormal response (Levy). Of the seven, there were four in whom there was acceptable evidence of past coronary disease. Three gave an "abnormal" response. The patient who gave a "normal" electrocardiographic response (Case 30) was in such profound anoxemia that we felt impelled to interrupt the test at the end of fifteen minutes. This patient probably had had coronary occlusion about five years before the test, and certainly has coronary artery changes, yet the electrocardiographic response was comparable to that of normal persons. Levy[37] stressed that a positive test indicates coronary insufficiency, but that a negative test does not rule out that possibility, and explains[16] some of these negative (normal) responses as instances of "coronary spasm initiated by nervous reflexes." He stated that, in these cases, "the reduction in coronary reserve was not sufficiently great to be indicated by the test," or that the heart muscle lesions lie in "silent" areas with respect to the electrocardiogram.

Wood and Wolferth,[38] who studied conventional leads only, noted significant electrocardiographic changes in only about 50 per cent of the patients during anginal attacks. They stated: "The absence of EKG change during an attack of angina pectoris cannot be used as evidence that temporary myocardial ischemia did not occur." A "normal" response to anoxemia in these cases in which there is acceptable evidence of a previous coronary occlusion may indicate adequate coronary anastomoses. That such anastomoses not infrequently occur in the arteriosclerotic heart was proved by Herrick[46] nearly thirty years ago, and by Gross,[47] in 1921, and has been more recently demonstrated by Schlesinger[42] and by Blumgart and his associates.[41]

Since the anoxemia test is designed to furnish objective evidence of coronary insufficiency, *a negative or "normal" response in a patient who presents equivocal evidence of coronary disease adds little to the diagnosis and may further cloud the clinical picture.*

We encountered a positive ("abnormal") response in two cases (Cases 8 and 128) in which satisfactory evidence of coronary insufficiency was lacking. In view of the fact that abnormal responses were obtained in some of our normal subjects, a diagnosis of coronary insufficiency does not appear justified in these cases.

TABLE V

PERSONS SUBJECTED TO ANOXEMIA INDUCED BY INHALATION OF A 10% OXYGEN MIXTURE

(Not Included in Normal Series)

NO.	AGE (YR.)	INITIALS	SEX	EXAM.	EKG	PAIN PRIOR TO TEST			PAIN DURING TEST					VASOVAGAL				CEREBRAL						EKG RESPONSE			
					CONTROL	PAIN—TYPICAL	PAIN—ATYPICAL	DYSPNEA	PAIN	DISCOMFORT	NERVOUS	RESTLESS	DYSPNEA	PALLOR	FALL IN PULSE	FALL IN B. P.	SYNCOPE	DIZZINESS	HEADACHE	CRANIAL CONGESTION	MUSCLE TWITCH	CONVULSIONS	FAIL RESPONSE	TEST COMPLETED		TEST INTERRUPTED	
																								N	Ab	N	Ab
														Group I													
														Subjects Excluded Because of Pain or Dyspnea													
8	53	R. G	M	N	N		+																				
169	64	J. L.	M	N	N		+		+																+		
26	35	F. K.	M	N	N		+																			+	
116	57	T. M.	M	N	N		+		+															+			
67	32	A. M.	M	N	N		+		+															+			
79	39	J. T.	M	N	N			+	+																	+	
96	45	L. A.	M	N	N		+			+																+	
100	49	J. L. K.	M	N	N	+			+																	+	
128	50	E. B.	F	N	N		+		+															+			
135	40	M. T.	M	N	Ab																				+		
187	56	C. A.	M	N	Ab																			+			
125	64	E. B.	M	N	N		+			+		+												+			
161	58	E. O.	M	N	N			+					+						+		+				+		
181	55	A. S.	M	N	N		+																		+		
35	37	J. McP.	M	N	N																			+			

Group II

Normal Subjects Showing Vasovagal and Cerebral Reactions

68	30	J. K.	F	N	N									+	+	+	+						+			+		
69	25	H. H.	F	N	N									+	+	+							+	N.R.	N.R.	+	N.R.	N.R.
121	49	G. P.	F	N	N									+	+								+			+		
143	41	C. E.	M	N	N									+	+	+							+			+		
152	54	M. J.	F	N	N		+							+	+	+	+						+			+		
167	40	C. W.	M	N	N									+	+	+					+					+		
172	54	E. B.	F	N	N																	+				+		
136	47	A. W.	M	N	N																	+				+		
165	54	E. L.	M	?	N																		+			+		
138	47	J. S.	M	?	N																		+			+		
119	54	L. J.	M	N	N									+	+	+				+						+		
98	17	B. McC.	M	N	N													+						+				
6	37	P. G.	M	N	N																							

Group III

Normal Subjects in Whom Test Was Interrupted Because of Development of Unfavorable Manifestations (Miscellaneous)

77	33	E. H.	F	N	N						+	+														+		?	
97	31	G. R.	M	N	N						+														N.R.	N.R.	N.R.	N.R.	
102	30	V. C.	F	N	N																						+			
112	58	H. K.	M	N	N		+				+														N.R.	N.R.	N.R.	N.R.	
126	56	C. B.	M	N	N		+					+															+			
137	54	H. McL.	F	N	N								+												N.R.	N.R.	N.R.	N.R.	
171	49	M. H.	F	N	N							+															+			
168	33	V. G.	M	N	N		+					+													N.R.	N.R.	N.R.	N.R.	
189	56	M. B.	F	N	N						Smothering		before		10%	O_2									N.R.	N.R.	N.R.	N.R.	
180	54	J. R.	M	N	N																									

Group IV

Persons Showing Some Evidence of Cardiovascular Abnormality

95	48	C. S.	M	Ab	N				+			+								+						+		
30	63	M. T.	F	N	Ab																					+			
37	50	H. B.	M	N	N																					+			
29	52	A. B.	M	Ab	N		+				+											+		?				+	
174	54	H. N.	M	N	?		+						+												+				
124	44	M. N.	F	?	?																			+			+		
56	25	M. F.	M	N							+																		
		45 cases				1	15	2	7	5	6	3	2	7	7	6	2	1	2	1	3	2	9	9	6	22	1		

N, Normal; Ab, abnormal; N.R., no record.

In a group of forty-five patients (not included in the normal series), with and without objective evidence of heart disease, there were sixteen who complained of pain which was sufficiently suggestive to warrant investigation, and they were subjected to anoxemia. Of these, nine complained of pain during the test, and in six, in our opinion, this was sufficiently severe to warrant interruption of the test.

In the three subjects who complained of pain or discomfort during anoxemia, but completed the test, one electrocardiographic response was normal and two were abnormal. Seven subjects had complained of pain but did not experience it during the test; the electrocardiographic (completed test) response was normal in one and abnormal in two, and, in the incompleted tests, normal in one and abnormal in one. No record was obtained in two of these cases. From this small group of cases it appears that, although pain may occur and interfere with the completion of this test, *the occurrence of pain during the test is not of much diagnostic value.*

Others[4, 14, 16, 27] have noted the variability of the occurrence of pain during anoxemia, but there appears to be no agreement as to the degree of anoxemia required to produce pain, and its bearing on the safety of the test.

Not one of the nine who complained of pain during the test showed evidence of cerebral anoxemia, as indicated by failure to respond to stimuli. It is possible that this might have been noted in some of the six tests which were interrupted because of pain.

Of the seven patients who had either a satisfactory history or signs of cardiovascular disease, three (Cases 30, 56, and 174) developed evidence of cerebral anoxemia which caused us to interrupt the test. Muscle twitching also occurred in Case 125, but, although the test was completed, we wonder, in retrospect, whether this was justified.

Evidence of cerebral anoxemia was a cause for the interruption of fifteen anoxemia tests. In nine there was failure to respond to visual or auditory stimuli. In five instances, muscle twitching, increasing to generalized convulsive movements, developed. In two instances convulsions occurred, at five and fifteen minutes, respectively, in subjects who had no evidence of cardiovascular disease. In each the convulsion was terminated by inhalation of oxygen. An interesting point in connection with these five cases is that, in spite of repeated responses to stimuli, these patients went into a convulsive state without premonitory manifestations.

Nearly twenty years ago, Haldane[44] warned that, when certain persons are subjected to anoxemia, there is little warning before actual unconsciousness occurs. Levy[37] reported two instances of convulsions during the test. It appears evident from even this limited number of cases that constant observation during the test for evidence of cerebral anoxemia, as indicated by failure to respond to stimuli, may not prevent the development of a sufficient degree of cerebral anoxemia to lead to con-

vulsions. Hartman[20] has called attention to residual changes in the brain after even short exposures to anoxemia; these changes consist of perivascular hemorrhage, edema, and vacuolation, with resulting degenerative changes in the substance of the brain. It would appear that this might possess potentialities which we would not wish to introduce as a side effect of a diagnostic procedure.

REGARDING HAZARDS INCIDENTAL TO THE ANOXEMIA TEST

Although the majority of the subjects completed the test without any symptoms which caused them or us any concern, we have encountered untoward symptoms in seventeen instances in a total of 189 tests. In all but two of these instances we felt impelled to interrupt the test. Of this total number of cases in which such manifestations occurred, five had symptoms of such severity as to furnish cause for alarm. We wish, therefore, to discuss at this point certain dangers which are incidental to this test even when it is carried out with the most meticulous care, for under no other conditions should any normal person be subjected to induced anoxemia, and this applies more forcibly to the subject with possible coronary insufficiency.

In a clinical experience of more than thirty years (C. T. B.) there have been numerous instances of acute heart strain associated with a change from sea level to Denver, and also with changes from the altitude of Denver to still higher altitudes. With more rapid means of transit, by streamlined trains which go from what is practically sea level to a mile-high elevation within seventeen hours (with 80 per cent of this ascent within less than nine hours), and by airplanes which cover the same distance within five and one-half hours, this hazard is of increasing importance. The hazards of air travel have been discussed previously.[15, 27] White[23] reported the death of a 27-year-old air corps pilot from coronary thrombosis very shortly after a flight which probably did not exceed 5,000 ft. in altitude. All previous history and examinations had indicated that he "was considered one of the better physical specimens in a group of highly selected and physically fit individuals." When he took off, he appeared to be perfectly well; on landing he was acutely ill and died within three hours. It was learned later that he had been taking sulfanilamide, which may have been a factor in the production of anoxemia, but it is certain that the cardiac accident occurred while he was in the air.

A 12 per cent oxygen mixture at Denver furnishes conditions equivalent to an altitude of 19,400 ft., and a 10 per cent mixture, to one of 23,500 ft. (at sea level, to 19,200 ft.). Either altitude is rarely attained in commercial air flights and never in this part of the world in travel by train, but in this test the subject is exposed very shortly after the beginning of the procedure, and for nearly twenty minutes, to the equivalent of an altitude of 19,200 to 23,500 ft. Both cardiovascular and cerebral disturbances have occurred in the course of induced

anoxemia tests. Levy, et al.,[16, 27] reported three instances of acute pulmonary edema, one of which developed after six minutes of 12 per cent oxygen (altitude, 16,000 ft.); in another, the patient was in shock after ten minutes of anoxemia (percentage of oxygen not stated). These two instances were encountered in men of 65 and 61 years, respectively. Acute pulmonary edema represents an extreme stage of failure. Minor evidence of failure is difficult to recognize early but, when once established, may progress to an extreme stage in a very short time. How many cardiac patients may experience slight degrees of failure induced by this test can only be conjectured at this time. We have been fortunate in that in none of our untoward results has failure been an apparent factor.

In a recent paper, Gross and Sternberg[40] pointed out that, in the course of certain functional disturbances, "circulatory disturbances severe enough to cause necrosis of the cardiac muscle" may occur, even in the absence of any demonstrable vascular lesion. As examples of such functional disturbances they cite "fall in aortic blood pressure as in peripheral shock, and phasic variations in the coronary flow"; and say that, in pathologic states, "the systolic coronary flow may provide the major nutrition of the heart." Blumgart, et al.,[41] stressed the "importance of avoiding fall in blood pressure from any cause in coronary arteriosclerosis." In certain instances we have noted a sudden and profound reduction of the blood pressure, which, though transient, might furnish the precipitating factor leading to infarction.

In animal experiments, partial to complete heart block has been produced by anoxemia.[31, 33, 45] Bundle branch block was described by Resnik,[1] who has observed bundle branch block and auricular and ventricular fibrillation during *experimental* anoxemia. We have not seen any of these conduction or rhythm disturbances, but the possibility of their occurrence during the test appears to present an incidental hazard.

Less dramatic than these instances of muscle or conduction system failure are certain vasovagal and cerebral manifestations which others[27] and we have observed. Reasoning from observations made in the course of aviation studies, and from the studies of Schneider and Lutz,[18] in 1920, Armstrong and Heim[24] stated that there are two general types of reactors to anoxemia, "fainters and nonfainters." They stated: "The fainters are those in whom the lower centers which control heart rate, vascular tone, and the rate and volume of breathing, suffer paralysis before the higher or psychic centers are affected. The non-fainters exhibit a failure of the psychic centers before the cardiac, vasomotor, and respiratory centers become seriously affected." They had noted sudden unconsciousness without any preceding evidence of abnormality. In our experience, fainting was not an uncommon occurrence. In a series of 132 normal persons, we noted a sudden fall in pulse rate and blood pressure, and pallor and/or syncope in seven cases. Table V presents in detail these signs and symptoms of vasovagal disturbance. Although none of these

proved to be at all serious, and cleared up immediately under oxygen administration, there is evidence of a profound involvement of the higher centers in these cases. Many of these vasovagal reactions occurred in psychoneurotic persons. McFarland[25] believed that this type of person is more susceptible to oxygen lack than normal subjects and that their cardiovascular reactions are subnormal. With both of these views we agree. He encountered fainting more frequently in the younger subjects. We have been surprised to note this and other vasovagal manifestations as frequently in the normal subject over 40 years of age as in our younger group of normal persons.

We have often had tests interrupted by the patient. Although this seems to be due to lack of cooperation, it may represent evidence of cerebral anoxemia, for mood and memory changes occur during generalized anoxemia.[19]

Vague symptoms suggesting coronary insufficiency frequently occur in the psychoneurotic person. Some objective evidence is especially desirable in these cases, but we have been obliged to interrupt the test, or it has been interrupted by the patient's removal of the mouthpiece, in about 50 per cent of the tests on subjects of this type. Since the time consumed in this test and the expense are factors, we consider the induced anoxemia test of doubtful value in this type of person.

Armstrong and Heim[24] stated that, at 14,000 ft. and above, "there is a progressive deterioration of voluntary muscular control," evidenced by "incoordination of finer muscular movements—slowing of movements, tremor and final paralysis." Experimentally, in guinea pigs and cats, and with higher degrees of anoxia,[22] spasmodic movements varying from isolated clonic twitching to generalized convulsions have been observed. Most of these changes are probably reversible, but there is evidence, as pointed out below, that this may not always be the case. In five instances, muscular twitching occurred in the course of anoxemia and, in two of these, progressed to generalized convulsions before the anoxemia could be terminated by oxygen inhalation. This appears to us to present a real hazard, for it has been shown that functional, and even structural, changes may take place in brain tissue during even brief exposure to anoxemia.[22]

That the brain is especially vulnerable to oxygen lack has been amply demonstrated in the course of recent studies, especially those concerned with the shock therapy of schizophrenia.[26, 32] Experimentally it has been shown that under anoxia both parasympathetic and sympathetic centers are excited to a varying degree and that mood and memory changes develop under 8.5 per cent oxygen.[19] Hartman[20] has shown that, in the anoxemia associated with shock, sedation, and fever therapy, perivascular hemorrhage, pericellular edema, vacuolation, and degeneration occur.

It is true that the time element in this type of therapy differs from that in the test under discussion, and that it is not customary to

subject anyone to anoxemia a second time within a twenty-four-hour period; this point has been stressed by Levy.[16] But even with slight anoxia (degree not given), Hartman[21] stated that one may encounter later neural lesions. Experience with aviators who have subjected themselves to repeated exposure to low oxygen tension suggests the possibility that a lowered cerebral reserve may account for the fact that, as their air experience increases, their ability to fly at high altitudes (without oxygen) diminishes.[22]

At oxygen partial pressures equivalent to an altitude of 28,000 ft. it is stated that cortical changes occur.[22] Some of these changes may become permanent. This is a lower oxygen pressure than that usually and intentionally employed in this test but not lower than that employed by mistake in six of our tests. We have mentioned an error (manufacturer's) in the oxygen percentage which occurred at an early stage in the work. Six persons were subjected to a mixture containing 8.6 per cent oxygen (equivalent to an altitude of 31,000 ft. approx.) before the error was discovered. Since that time the contents of each tank have been analyzed before use and re-examined if there was any cause for question. All of these subjects showed evidence of extreme anoxemia. In two instances the test was interrupted at three minutes (Case 42) and at twelve minutes (Case 43), respectively, because of suffocation. One subject (Case 41) had slight blurring of vision and headache at twenty minutes, and one (Case 40) at nineteen minutes failed to respond to stimuli and had a generalized tremor; but in both cases the electrocardiographic response for the completed test over a twenty-minute period of such high-grade anoxemia was normal. The four above-mentioned subjects were "normals" between the ages of 21 and 30 years. Preceding the four tests just mentioned, we had subjected two older men to this test. Case 38 (aged 45 years), who was normal on physical and electrocardiographic examination, was born and lived for seventeen years at an elevation of 9,577 ft.; since that time he has lived mainly at this mile-high elevation and is accustomed to mountain activities. He reported a sensation of plugging in the ears which was comparable to what he had noticed on several occasions when he was exposed to reduced barometric pressures. He stated that he experienced some discomfort during the test and felt definitely shaky after it. He had a throbbing headache which lasted all evening and even some "hangover" the next morning. His completed test showed an abnormal response, according to Levy's Criterion 1, and was questionable with respect to Criteria 2 and 4. Case 39 (aged 47 years) has resided in Denver for fifteen years. We learned later that he had some hypertension, without other evidence of cardiovascular abnormality. He reported that he felt as if he were close to the initial stages of anesthesia toward the end of the test. He was also quite uncomfortable and had some headache afterward and some "hangover" the next day. His completed test showed an abnormal response according to all four

of Levy's criteria. These two men are experienced physiologists whose observations we consider dependable. Consistent with their observations are those of McFarland,[25] who stated: "In the subjects who collapsed, the headaches, nausea, palpitation, pain in the chest and muscular twitchings lasted from one to ten hours. Even in several of the subjects who reacted easily, some of the after-effects mentioned above were noticeable for one to two hours later."

These experiences were so impressive that we took care to ensure accuracy in our gas percentages. It is a matter of interest that but one of the six men who were subjected to this extreme grade of anoxemia showed muscular tremor, and none had convulsive movements, although four were carried through twenty minutes of anoxemia, which is equivalent to an altitude of 31,000 ft. (approx.). These observations are in accord with those of Michelson and Thompson,[28] who found that the degree of anoxemia does not bear a quantitative relationship to the severity of the clinical manifestations, for, under identical conditions, the arterial oxygen saturation may vary in different persons. But that such a degree of anoxemia may produce distinct morphologic changes appears to be proved. In the individual case there seems to be no means of predicting whether such damaged cells can recover.

There are certain physiologic responses which tend to offset the unfavorable cardiac and cerebral responses above mentioned. McFarland[25] quoted a French investigation in which it was found that the carotid body is especially sensitive to anoxemia and that, when so stimulated by a relative excess of carbon dioxide, there is a compensatory increase in circulation and respiration; "thus more oxygen is supplied to the deficiency of the respiratory, cardiac and vasomotor centers." Wiggers[34] stated that, contrary to data in the literature, anoxemia has a stimulating effect on the heart and that the economy of the ventricle is improved under such degrees of anoxemia as are being discussed here. If this is correct, it would seem that evidence of cerebral and myocardial ischemia should never occur under conditions of anoxemia.

DISCUSSION

We have presented the results of a series of observations on 125 persons who were entirely normal from the cardiovascular standpoint and were subjected to anoxemia induced by the inhalation of a 10 per cent oxygen mixture. These studies lead us to believe that there is a usual, or "normal," response, consisting of practically no symptoms, but of certain rather definite changes in the electrocardiographic pattern which are promptly reversed by the inhalation of oxygen. These changes have been presented clearly in tables and charts. In spite of the generally accepted view that some physiologic change occurs in the coronary vessels in the later decades, we found no significant difference in the electrocardiographic responses which take place in persons 50 to 60

years of age, as compared to the three preceding decades. We have described a usual, or "normal," response. However, in a significantly large group (19.2 per cent) of subjects whose history, physical and electrocardiographic examination, and response to exercise were normal, who were, in fact, by every usual clinical standard, considered normal, we found an electrocardiographic response which has been described by Levy[4, 16] as indicative of coronary artery insufficiency. We believed that Levy had demonstrated the value of this procedure in clinical diagnosis, although, as stated before, we were dissatisfied with the basis for his normal criteria. As this work progressed we reluctantly came to the conclusion that a test which gave an "abnormal" response in 19.2 per cent of normal persons, and as frequently in the younger age groups as in the last decade studied, would be of doubtful clinical value. After eighteen months of experience we have had frequent failures due to technical error or lack of cooperation on the part of the subject. Unpleasant or even alarming symptoms occurred in sixteen instances. That there is some correlation between the efficiency of the coronary circulation and the electrocardiographic response seems apparent, but we have encountered "abnormal" responses in normal subjects and "normal" responses in abnormal subjects too frequently to justify, in our opinion, the use of this test as it is at present employed in clinical diagnosis.

If there is a difference between the responses of persons living at sea level and those residing in Denver, we wish to point out that a smaller number of normal persons should show an "abnormal" response at the high altitude than at sea level, for this group has been acclimated to low oxygen tension.

This work may be criticized because of the actual oxygen want to which the subjects were exposed, due to the lower partial pressure of our atmosphere. We exposed our subjects to greater anoxic strain than Levy did at sea level, but this strain was not as great as the difference in partial pressure would indicate. This, we believe, is compensated partially by residence in this altitude, but, if this is not the case, it would seem that our group of cardiovascular patients should have shown a more unfavorable and more consistently abnormal response than they did.

The accepted idea that some degree of coronary artery change is associated with the aging process is not supported by these studies. This means either that the induced anoxemia test is not a dependable means of demonstrating coronary artery disease, or that such disease does not consistently occur in the later decades. We favor the former opinion.

In 1928, Keefer and Resnik[5] wrote: "Unfortunately there is not at present an absolute criterion of the diagnosis of angina pectoris—the decision in an individual case must be determined by the outcome." In the utilization of induced anoxemia it has been thought that we may

very well be approaching that "absolute criterion." The results of our investigation appear to leave us in the same position as that of Keefer and Resnik, in 1928.

CONCLUSIONS

1. The data which have been presented describe the "normal range" of electrocardiographic response to induced anoxemia in clinically normal subjects.

2. These electrocardiographic changes progress with the continuation of anoxemia but are promptly reversed by the inhalation of 100 per cent oxygen.

3. There was practically no difference in this response in the various age groups studied.

4. A different response was encountered in 19.2 per cent of clinically normal persons. This response has been described elsewhere as indicative of coronary artery insufficiency. We are not in accord with this idea.

5. Induced anoxemia cannot at the present time be considered a routine laboratory procedure which is devoid of all danger to the patient and free from the possibility of misinterpretation of electrocardiographic changes.

6. We feel that a word of warning is in order regarding the application of this test in clinical investigation. Meticulous care in the selection of the subjects, and especially in the performance of the test itself, will prevent some of the unpleasant experiences noted by others and ourselves. To this end, teamwork is essential. For the present the test should be considered as strictly a hospital procedure.

To Dr. Robert L. Levy we wish to express appreciation for the most cordial cooperation, and to Professors R. W. Whitehead and William Draper, of the Department of Physiology and Pharmacology, for helpful advice and criticism. To Mrs. Marie Williams we are indebted for untiring technical assistance.

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DISCUSSION

DR. DAVID MILLER, New York, N. Y.—Dr. Burnett's excellent studies raise a question—and I wonder whether he has any comment on this question—whether, in subjecting a normal heart to low oxygen tension, one may not be dealing fundamentally with the effect of deprivation of oxygen on central autonomic nuclear masses, rather than on the heart, or perhaps both. The responses which Dr. Burnett elicited seem to indicate that, with this low oxygen tension, the upper level of the brain and the brain stem are particularly concerned with the autonomic control of the cardiovascular apparatus. It is now known to physiologists that different levels of the brain stem and cortex react best at certain different, and specific, oxygen concentrations.

However, without laboring the point, it seems to me that in this kind of test the normal subject may be reacting primarily by virtue of some change in his heart muscle, or that the cardiac effect may be only a localized expression of a much more extensive autonomic effect. If we, as clinicians, are to employ a test of this character, we must be certain that the effect is chiefly and primarily on the heart and not widespread and generalized.

The second point I want to talk about is the matter of syncope in association with cardiovascular states. It is a commonplace that, when there is cardiovascular depression, syncope is very likely to occur, but syncope may also occur without cardiovascular depression. Stimulation of the labium cerebri will produce very marked signs of cardiovascular depression but no syncope. On the other hand, stimulation of the trigon zone has often produced a marked change in the cardiovascular apparatus. It is possible to produce cardiovascular changes, without syncope, by stimulation of higher areas in the cerebrospinal system.

It seems to me that this raises an important point. It is practical for us to consider whether there may not be a separate mechanism which is responsible for syncope, just as the effects of impulses from the periphery of the body which lead

into the neuraxis are referred to as cardiovascular changes. Is it not possible that syncope is the result of stimulation of specific areas of the neuraxis? If so, the mechanism is distinct from others.

DR. DOUGLAS DEEDS, Denver.—Dr. Burnett and his co-workers are my colleagues at the University of Colorado School of Medicine, and I am happy to have this opportunity of congratulating them on the tremendous amount of work they have done on this subject.

I have been doing Levy tests on my private patients at our mile-high altitude, also. I have not encountered any untoward reactions even in bona fide abnormals, and do not consider the test dangerous.

To aid in acquiring a better understanding of my results, tests were done on myself at sea level by Dr. Levy, with a 10 per cent oxygen mixture, and later the process was repeated at mile-high altitudes with the same 10 per cent oxygen mixture. Objectively there was no significant difference, but subjectively the difference was considerable. Because of my studies I should like to suggest that, before we conclude that the Levy test is an unsatisfactory and dangerous test at our altitude, we must run another series of tests, using a 12 per cent instead of a 10 per cent mixture, to see whether the same untoward reactions and T-wave inversions occur.

I say this because, in discussing this matter with competent authorities, I am told that the oxygen saturation of hemoglobin (which varies greatly with changes in atmospheric pressure) is the important feature and that a person who lives at our altitude is not able to compensate completely for the difference in atmospheric pressure, regardless of his length of residence.

In Denver we are exactly one mile above sea level and have an average atmospheric pressure of 627 mm. of mercury; at sea level the latter averages 760 mm. For practical purposes this means that, gasometrically, 10 per cent of oxygen at sea level is equivalent to 12 per cent of oxygen one mile above sea level. Similarly, 8 per cent of oxygen in New York City is about equivalent to 10 per cent in Denver.

In my opinion, if Dr. Levy's normal standards, established in New York, are to be applied at our altitude, we should use 12 per cent and not 10 per cent oxygen mixtures. If Dr. Levy had used 8 per cent oxygen mixtures in establishing his standards, he, too, might have encountered the high incidence of untoward reactions and T-wave inversions in Lead IVF which have just been described by Dr. Burnett.

Certainly, we need some method of diagnosis which is more accurate and helpful than our clinical opinion, plus the resting electrocardiograms, in diagnosing preocclusive coronary sclerosis. Despite its disadvantages, to date, the Levy test has answered this real need better than any previous diagnostic adjunct. Although I shall retain the open mindedness which I have always had regarding such diagnostic aids, I plan to continue my use and scrutiny of the Levy test, for only by the continuation of such studies will we lessen a serious diagnostic weakness.

DR. LOUIS N. KATZ, Chicago.—Considering the potential hazards of anoxemia, which we also noted several years ago, I feel strongly that patients with suspected coronary disease should not be subjected to this test routinely.

DR. CLOUGH T. BURNETT.—In a letter to me Dr. Levy raised the question whether our records were not vitiated by an experience similar to one I mentioned at the meeting of this Society last year in connection with the discussion of his paper, namely, an error in the percentage of our oxygen. This will be discussed when our paper is published, but was not mentioned in that portion just presented. Six persons, through the manufacturer's error, were consecutively subjected to an 8.6 per cent oxygen mixture before the error was recognized. I can assure those here,

and assure Dr. Levy, that that error occurred in only six instances, but it was not until the sixth that we realized that something was wrong. Since then, repeated gas tank analyses have prevented further errors of this sort.

Dr. Levy raises a question, as does Dr. Deeds, as to the elevation at which we are working. Theoretically, we did place these subjects under a greater strain than does Dr. Levy, but we maintain that one who has resided at a mile-high elevation for at least several months—and many of our subjects have lived there for years—has become acclimatized to low oxygen pressure, and that fact should be taken into account.

Dr. Deeds has mentioned the difference in the response to the test as done in New York and as done in Denver. Dr. Nims, one of my collaborators, had a test run in Dr. Levy's laboratory, as well as one in Denver, and he did not notice any difference. I have never been tested at sea level. I was tested in Denver and was one of the easy and normal reactors. Personally, I should just as soon do it again tomorrow, because I know how I reacted. The difficulty is that we cannot predict which subject will have syncope, which will develop vasovagal reactions, and which will have convulsions. Until we can work out some means whereby that can be satisfactorily known, I believe there is a hazard which prevents the ready acceptance of this test in clinical diagnosis.

Dr. Miller has discussed the autonomic responses. These occurred unpredictably. Age did not seem to make any difference. When we finally completed our work, we did not feel that, with the initiation of any test, we could tell whether we were going to be able to complete it or not. We should be open minded, but I believe that, when a team which worked as long as we worked on this investigation continued to encounter the difficulties we did, and when, in addition, the interpretation of the response is subject to a considerable element of error, the test is of doubtful value in clinical diagnosis.

A METHOD FOR PERFUSION OF RABBITS' EARS, AND ITS APPLICATION TO STUDY OF THE RENIN-ANGIOTONIN VASOPRESSOR SYSTEM, WITH A NOTE ON ANGIOTONIN TACHYPHYLAXIS

IRVINE H. PAGE, M.D.
INDIANAPOLIS, IND.

STUDY of the renin-angiotonin vasopressor system has been facilitated by a method with which isolated organs can be perfused with both blood and Ringer's solution, employing a pulsatile pressure. For most investigations, the rabbit's ear has proved to be the organ of choice. The purpose of this communication is to describe this method in detail, so that it can be reproduced when sufficient dexterity is achieved.

It may interest the reader if the field to which the method has been applied is briefly outlined. Purified renin exhibits no vasoconstrictor properties when it is perfused through a rabbit's ear in Ringer's solution,[1] but, when a fraction of the pseudoglobulin (tentatively called renin-activator)[2, 3] of the blood is added, interaction occurs, and a third substance is formed which causes vasoconstriction. A thermostable substance was isolated, crystallized, and termed angiotonin.[4, 5] But angiotonin itself is probably unable to act in a rabbit's ear perfused with Ringer's solution in the absence of a substance in the plasma which has been called angiotonin-activator.[6]

Kidneys in which the pulse pressure has been reduced liberate renin.[7, 8] It is our belief that this renin combines with renin-activator to produce angiotonin. In the renal veins, therefore, a mixture of renin and angiotonin may be found,[9] but in peripheral blood an "angiotonin-like" substance occurs.[10] The latter is detected by injecting plasma from a hypertensive dog into blood, being perfused through a rabbit's ear, from a dog in which both kidneys have been removed ("arenal" blood). This substance is much increased in animals with experimental hypertension, in patients with essential and nephritic hypertension, and in normal dogs and rabbits after the injection of renin. A somewhat similar line of reasoning has been developed by Munoz, Braun-Menendez, Fasciolo, and Leloir.[11]

Method for Perfusion With Pulsatile Pressure.—Two types of apparatus have been designed and built, chiefly by Mr. Clifford Wilson, of the Lilly Laboratory for Clinical Research, for perfusion of organs. The first type is simpler to construct but does not offer the flexibility of adjustment inherent in the second. Both types have proved very satisfactory in practice for four years.

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Pulsation is imparted to the air jet in the first type by means of a "windshield wiper" respirator, and, in the second, by a motor-driven cutoff valve.* The systolic

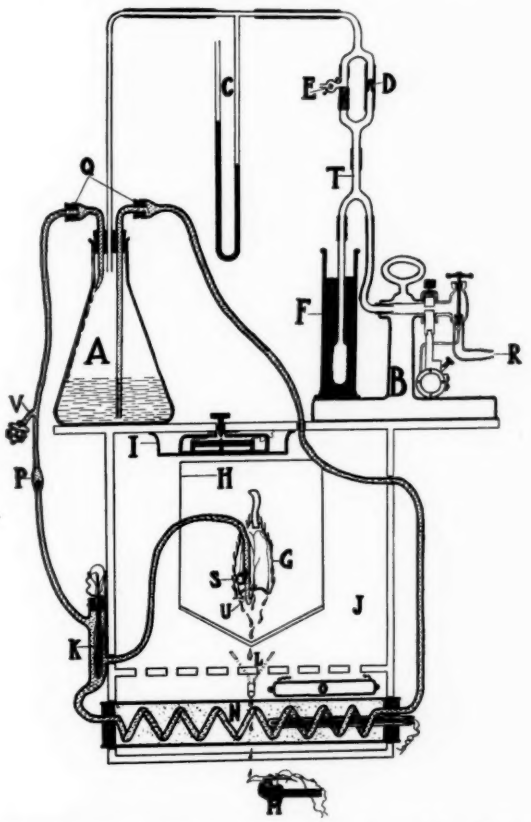

Fig. 1.—Pulsatile Pressure Apparatus. *A*, Ringer-Locke's solution reservoir (1,000 c.c.), fitted with a three-hole rubber stopper, through which pass three glass tubes (air pressure, fluid delivery, and fluid return tubes); *B*, artificial respirator ("windshield wiper" type to furnish pulse); *C*, mercury manometer; *D*, one-way air valve; *E*, pressure relief valve (when properly set, will allow air to escape from the system after each pulse, to give desired diastolic pressure); *F*, peripheral resistance (made by submerging a fast-filtering Berkefeld filter in mercury to a depth necessary to prevent the escape of air up to desired pressure, and to exhaust all air in excess; this pressure is the systolic); *G*, rabbit's ear; *H*, glass plate supported at 45° angle, upon which the ear is placed; *I*, thermoregulated incubator; *J*, thermostat for incubator; *K*, thermostat connected to cut off heater when perfusion fluid attains the desired temperature. More recently we have inserted this into tube *N*, instead of *K*; *L*, glass funnel to catch and guide fluid from ear to the drop recorder through funnel spout; *M*, drop recorder to measure flow through ear during perfusion; *N*, heater consisting of cylinder filled with water, both ends of which are closed with rubber stoppers; through these the glass coil carrying solution and heater are fitted; *O*, heater for incubator; *P*, one-way return cone valve to protect ear from back pressure when exchanging or circulating perfusate with the aid of a syringe connected at *V*; *Q*, one-way flap valves connected to the fluid delivery and fluid return tubes; *R*, air inlet (to be connected to constant-pressure air line); *S*, side arm fitted with serum bottle stopper, through which injections are made into the ear that has been cannulated; *T*, pulsating air jet; *U*, glass cannula inserted into the artery of the ear; *V*, T-tube for exchanging or circulating perfusate.

and diastolic pressure is regulated by a submerged Berkefeld filter in the first type, and by a rubber "peripheral resistance" in the second. Injections into the stream of fluid perfusing the ear are made through a serum bottle stopper, which is inserted into a side arm directly above the arterial cannula. The glass plate on which

*Arthur H. Thomas and Company—Respiration cutoff valve, catalogue No. 8107.

the ear rests is grooved so that all fluid issuing from the cut ends of the veins will run immediately into the collecting funnel and be recorded. It was found that the Ringer's solution, dropping on the electrical contact points, soon corroded them; hence, a flask filled with 500 c.c. distilled water, with a side arm from which the diluted fluid dropped onto a recorder, was inserted. The tipping-spoon type of recorder was found to be even more satisfactory. Accurate temperature control was achieved by thermostats in both the box housing the ear and the water baths containing the Ringer's solution reservoir. If blood is used as the perfusion medium, a Baxter wire-gauze filter, as used in transfusion sets, is inserted into the line delivering the perfusate to the ear. Not shown in either figure is a humidifier in the box containing the ear. It consists of a pan of water, covered with wire gauze on which surgical gauze is spread.

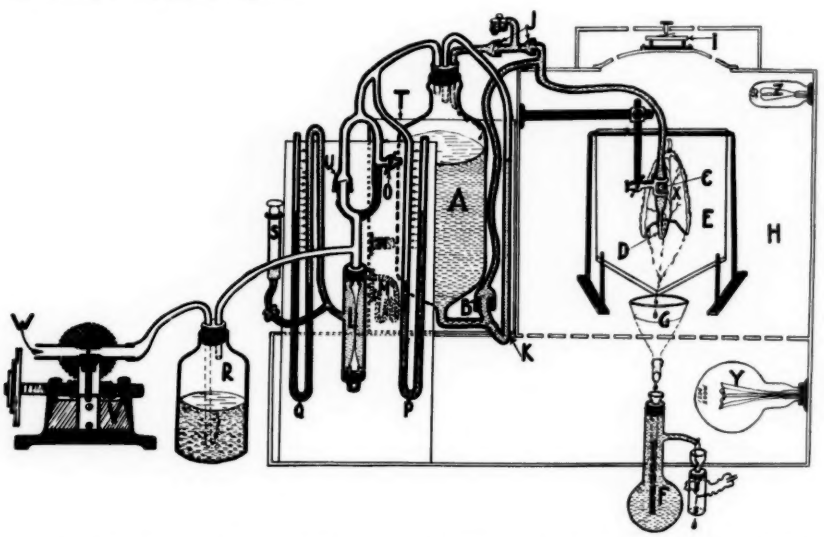

Fig. 2.—Pulsatile Pressure Apparatus. *A*, Reservoir for Ringer-Locke's solution; *B*, one-way valve; *C*, serum-bottle stopper fitted on side arm (through which injections are made); *D*, glass cannula (which is inserted into the artery at the base of an excised rabbit's ear); *E*, glass plate (supported on stand at 45° angle); *F*, flow recorder; *G*, glass funnel (to catch liquid flowing from ear); *H*, incubator (in which the temperature is regulated); *I*, incubator thermostat; *J*, one-way valves; *K*, reservoir gauge; *L*, peripheral resistance (this is made by stretching a thin elastic rubber tube through a cylinder; the pressure within this cylinder may be adjusted to any desired level); *M*, water-bath heater; *N*, water-bath thermostat; *O*, pressure relief valve (releases air in system in amounts necessary to establish desired diastolic pressure); *P*, manometer (records systolic and diastolic pressure in perfusion system); *Q*, manometer (records pressure exerted by peripheral resistance *L*); *R*, air-washing bottle; *S*, syringe (enables one to regulate the pressure exerted by liquid against rubber tubing in *L*, which is water cushioned); *T*, water bath (in which the temperature is regulated); *U*, one-way valve (through this valve air passes to the perfusion system; the amount of air passing to the system to build up pressure within it cannot exceed that of the peripheral resistance, thus establishing the systolic pressure); *V*, motor-driven cutoff valve (through which air blasts pass at regular intervals); *W*, air inlet; *X*, rabbit's ear (taped on glass plate); *Y*, incubator heater; *Z*, observation light (for ear compartment).

Construction of Valves.—Three different types of valves have been used in the construction of the perfusion apparatus.

1. Flap Valve (Fig. 3).—The construction of this valve is obvious from the drawing. The flap is made of rubber sheeting and is kept in place by a tiny bit of rubber cement on the edge. This valve facilitates thorough washing of the apparatus. It may be used with solutions which will corrode metals.

2. Cone Valve (Fig. 4).—A glass tube is heated at *D* until it melts sufficiently to thicken its wall. It is then pulled into a cone. Valve *C* is made from a glass

tube whose outside diameter will allow free movement within tube *B*. It is heated, pulled into a cone, and sealed with a heavy bead. The beaded tip is dipped into oil and emery, inserted into tube *B*, and ground until the joint fits smoothly. The valve is removed. All excess glass is cut off as close to the ground surface as possible. The valve is sealed, returned to chamber *B*, heated at point *A*, pulled out, and twisted into a spiral.

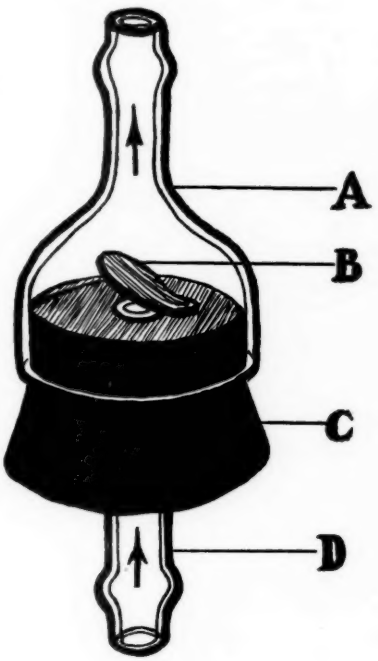

Fig. 3.

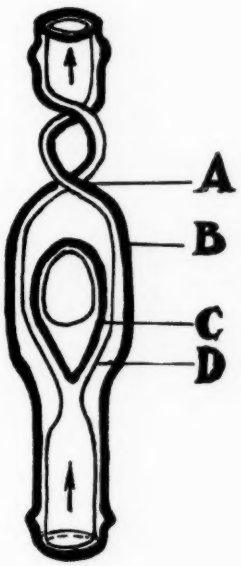

Fig. 4.

Fig. 3.—Flap valve.
Fig. 4.—Cone valve. *A*, Chamber outlet; *B*, valve chamber; *C*, valve; *D*, valve seat.

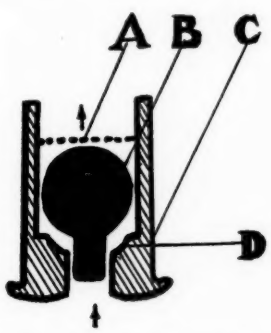

Fig. 5.—Air valve. *A*, Wire gauze; *B*, rubber or metal ball valve; *C*, cylinder containing valve seat *D*.

3. Air Valve (Fig. 5).—This type of valve is used only for air.

Preparation of Perfusing Media and Samples of Blood for Assay.—The renin employed was prepared by the method of Helmer and Page.[12] It was filtered shortly before use, for small particles of precipitate clog up the vessels of the

ear, thus simulating vasoconstriction. It was also necessary to dialyze it carefully, as undialyzed renin causes vasoconstriction. When perfused, it should cause no vasoconstriction.

Plasma was prepared for testing by drawing venous or arterial blood under oil into a syringe moistened with a solution of 50 mg. of heparin in 5 c.c. of isotonic saline, centrifuging, filtering the plasma, and storing at 10° C. Before being used, it was warmed to 37° C. and filtered through No. 42 Whatman filter paper. It was found that plasma could be kept for forty-eight hours, and perhaps longer, without losing its ability to activate renin. For the estimation of renin-activator, eight parts of plasma were mixed with one part of renin and allowed to stand at room temperature for ten minutes. The mixture (0.2 c.c.) was injected into the Ringer's solution perfusing the ear. Angiotonin-activator was estimated by first injecting small quantities of angiotonin until the vessels of the ear no longer responded by constriction. Plasma, usually 0.2 c.c., was then mixed with the standard dose of angiotonin and the mixture immediately injected.

Hemolyzed erythrocytes were prepared by first washing a weighed amount of cells with salt solution, hemolyzing with distilled water, bringing to isotonicity with salt, centrifuging, and filtering the supernatant fluid.

Tests were made on a fresh ear only when the drop rate was satisfactory (60 to 125 drops per minute with Ringer-Locke's solution) and were repeated when the original drop rate had been restored for at least five minutes. The whole experiment was usually finished within an hour and a half, for the ear tended to become edematous after this period. The amount of vasoconstriction was recorded both in terms of the length of time, in minutes and fractions thereof, which was required for the drop rate to return to its initial value, and the percentage reduction of drop rate. The percentage reduction was calculated by comparing the number of drops counted with a blood-cell counter during the period of vasoconstriction with the number during the period before the injection.

When blood was used as the perfusing medium, it was drawn from large dogs (18 kg.) from which both kidneys had been removed aseptically under pentobarbital sodium anesthesia (30 mg./kg.) twenty-four hours before. This so-called "arenal blood" was sometimes heparinized (88 units per 65 c.c.) and immediately diluted in the proportion of 1:3 with Ringer's solution. If it was necessary to allow it to stand before use, it was put in an incubator at 37° C. and, before use, was filtered through washed cotton gauze. Usually the arenal blood was defibrinated by shaking for seven minutes in a flask containing four spirals of copper wire which were prepared by winding the wire around pencils.

If the perfusion fluid to be employed was Ringer-Locke's solution, it was made fresh each day, as follows:

NaCl	9.00 Gm.
KCl	0.41 Gm.
$CaCl_2$	0.24 Gm.
$MgCl_2$	0.06 Gm.
$NaHCO_3$	0.50 Gm.
Dextrose	0.50 Gm.

Make up to 1 liter with distilled water, and add sodium bicarbonate and dextrose last. Filter before use.

Preparation of Ear.—The ear of a young rabbit was found most suitable for perfusion. It was sponged at the base with water at 50° C., and then with one swift cut was severed from the unanesthetized animal by means of a sharp scalpel (Fig. 6). It has been found that the rabbit bleeds less and recovers more rapidly from amputation of the ear if no attempt is made to tie off the

vessels. A tie or hemostat will be scratched off as soon as the rabbit is free. Incisions were made on both sides of the artery, and a small hemostat was placed in such a way as to grasp the cut end of the artery and keep it free. A small

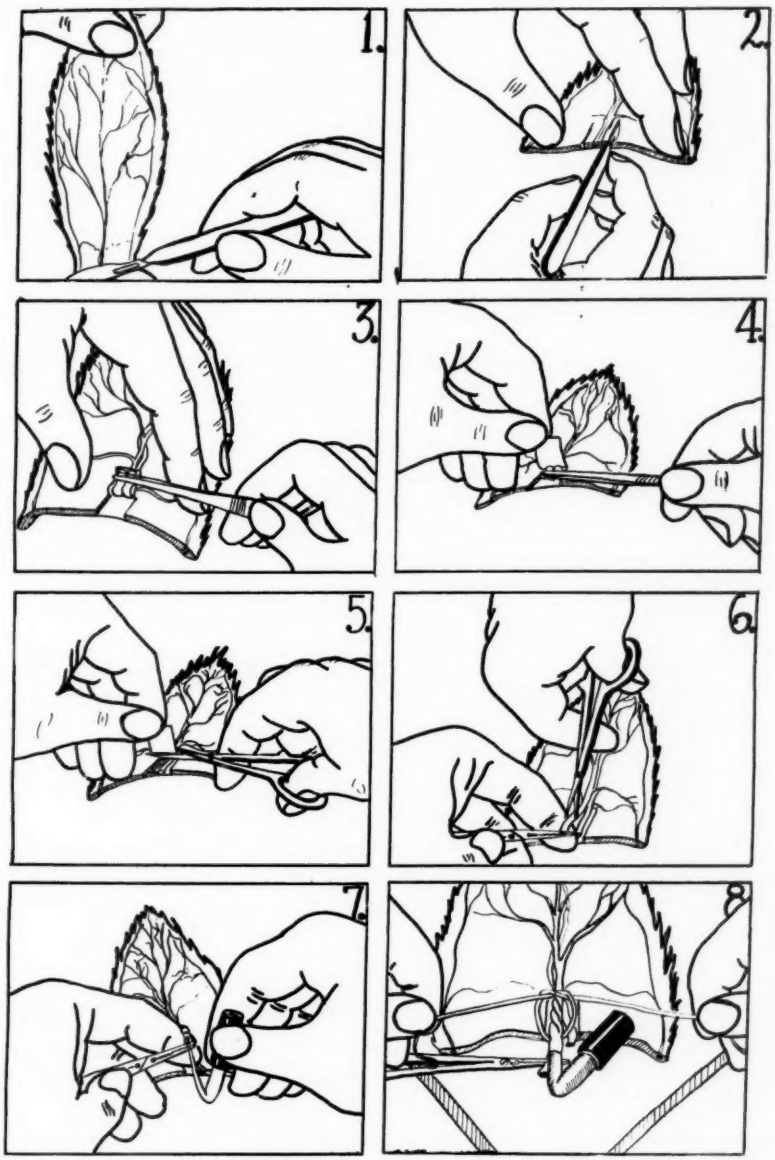

Fig. 6.—*1*, Severance of the ear with sharp scalpel. *2* and *3*, Dissection of artery and vein. *4* and *5*, Separation of vessels from skin flap. *6*, *7*, and *8*, Insertion of cannula. These operations must be performed quickly and gently. There must be no tension on the cannula, and the artery should not project beyond the cut edge of the ear, lest drying of the vessel occur.

incision was made in the artery, and a glass cannula was quickly inserted and tied with silk; care was taken to traumatize the intima as little as possible. Warm Ringer's solution was used to wash out the remaining blood and insure

the patency of the cut ends of the veins. The tissues separated from the artery were then cut away. This entire operation should not take more than two minutes. *Gentleness and speed are vital to the success of the preparation.*

The ear was then placed on the draining plate and secured with adhesive tape, and a piece of string was placed against the cut surface to lead the perfusate into the collecting funnel. The cannula was connected to the apparatus with rubber tubing, and the warm (37° C.) perfusion solution was allowed to flow through the ear under the desired pressure (20/10-30/20 mm. Hg for Ringer-Locke's to 60/40-80/60 mm. Hg for diluted blood). The position of the ear must be correct, i.e., the artery straight, but not tense or twisted, and the system free of air bubbles. Perfusion proceeded more satisfactorily if the ear was undisturbed for a period of fifteen to twenty minutes. The beginning drop rate was very slow (four or five per minute) but gradually increased until a rate of 90 to 120 drops per minute with Ringer-Locke's solution had been reached. The ear was then ready for use. The drop rate should remain nearly constant throughout the experiment.

The ear to be perfused with blood was first washed through with Ringer-Locke's solution for a period of twenty to forty minutes, and then diluted blood was substituted. The average drop rate with blood was 16 drops per minute.

The usefulness of the ear was usually terminated by the occurrence of edema. The addition of acacia (20 c.c. of 6 per cent solution) to the Ringer's solution perfusing the ear occasionally seemed to reduce the rate of edema formation. Doubling the concentration, however, did not further decrease it. Experience has shown that the increase in weight of a satisfactory ear preparation was not greater than 8 Gm. in two to three hours.

It has proved wise always to perfuse a sample of the filtered plasma alone, before the addition of renin, to ascertain whether it, of itself, causes vasoconstriction.

If the blood had hemolyzed, vasoconstriction occurred when 0.2 c.c. of plasma was injected, whereas the same amount of plasma without hemolysis caused no vasoconstriction. Ears occasionally were so sensitive that they responded with moderate vasoconstriction to plasma alone. Such preparations were discarded. It was important to filter the plasma, especially when it had stood overnight, before injecting it into the ear. Particles of coagulated plasma form and clog the small vessels, giving the impression that vasoconstriction has occurred. The drop rate in such cases did not return to its initial value after the injection.

ACTION OF PITRESSIN, METHYL GUANIDINE SULFATE, AND TYRAMINE

Perfusion with pitressin (0.1 c.c. of 1:200 dilution) caused definite vasoconstriction which might be reproduced many times without marked loss of vigor. The addition of plasma from either hypertensive or normal dogs did not enhance its action. Methyl guanidine sulfate (0.2 c.c. of 1:200 dilution) also produced definite vasoconstriction which was not enhanced by the addition of plasma. From twelve to twenty injections might be given without significant decrease in response. Doubling the amount of methyl guanidine did not produce twice as much vasoconstriction. Tyramine (0.2 c.c. of 1:2,000 dilution) was about ten times as active as the same amount of methyl guanidine sulfate. Its action was unaffected by the addition of plasma. None of these substances proved suitable as standards for renin and angiotonin.

OBSERVATIONS ON THE ACTION OF RENIN-PLASMA MIXTURES AND ANGIOTONIN

The first injection often produced less vasoconstriction than did subsequent injections. When Ringer's solution was employed for perfusing the ear, as many as twenty injections might be given without loss of vigor of the response. When blood was employed, usually ten to fifteen injections might be made without any change in the sensitivity of the ear. It was noticed that renin-plasma mixtures did not cause edema of the ear as rapidly as did the usual vasoconstrictor drugs.

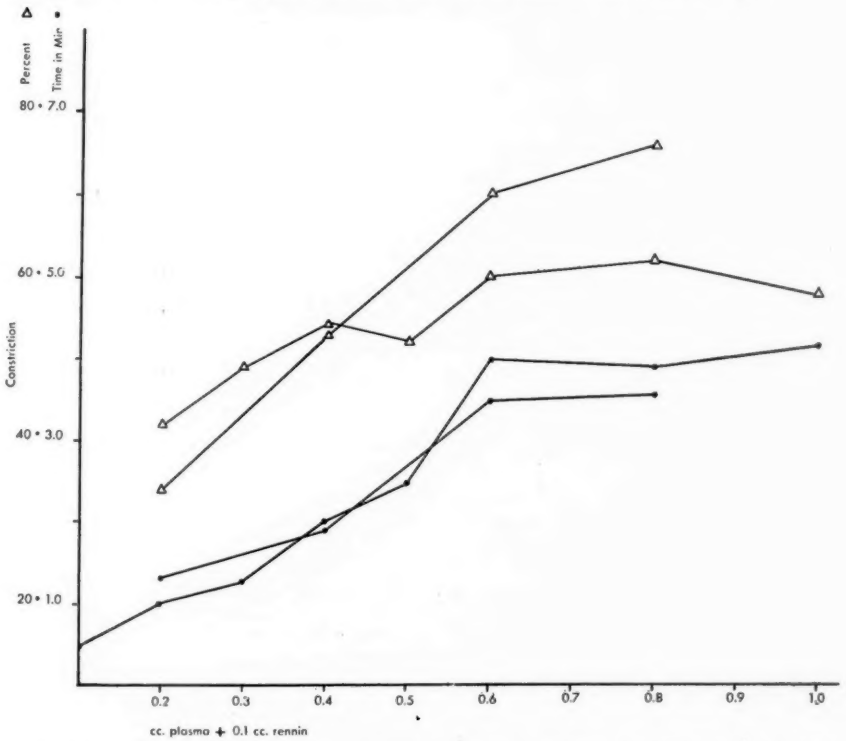

Fig. 7.—Relationship between vasoconstriction (percentage reduction of drop rate and time of reduction) and plasma-renin mixtures in which the renin is constant and the amount of plasma varied. These represent assays performed with the same renin-plasma mixture on the ears of two rabbits.

The first injection of angiotonin caused sharp vasoconstriction, the second, less, and the third, usually none. The addition of a small amount (0.2 c.c.) of plasma to the angiotonin restored the initial vasoconstrictor action.

When it was desired to ascertain the amount of renin- or angiotonin-activator in plasma, a standard amount of renin was mixed with increasing amounts of plasma until a level was reached at which further addition of plasma caused no marked increase in vasoconstriction (Fig. 7).

To compare one plasma with another for a semiquantitative estimation of activator, fixed amounts (0.2 c.c.) of plasma were mixed with excess, fixed amounts of renin; then the mixture was incubated for ten minutes and injected. Since renin was present in excess, if greater amounts of activator were present in one than in the other plasma, greater vasoconstriction resulted from the sample with the greater amount of activator.

TABLE I

THE COMPARATIVE VASOCONSTRICTOR ACTION OF PLASMA AND SERUM FROM A HYPERTENSIVE* DOG (NO. 9-73), AND THE EFFECT OF HEMOLYSIS

	DURATION OF REDUCTION OF FLOW (MIN.)	REDUCTION OF FLOW (%)
Ringer's solution perfused		
0.2 c.c. plasma	0	0
0.2 c.c. serum	0	0
0.2 c.c. plasma slightly hemolyzed	0.25	12
0.2 c.c. plasma grossly hemolyzed	0.5	18
Arenal blood perfused		
0.2 c.c. plasma	4	61
0.2 c.c. serum	4.5	64
0.2 c.c. plasma slightly hemolyzed	5.5	75
0.2 c.c. plasma grossly hemolyzed	7.5	79
0.2 c.c. plasma	4.25	60
Second rabbit's ear		
0.2 c.c. plasma from a second hypertensive dog	6.25	47
0.2 c.c. serum from a second hypertensive dog	6	50

*Silk perinephritis method.

The amount of renin in blood may be estimated by the addition of plasma containing activator or concentrated activator prepared from blood, until further addition causes no further increase in vasoconstriction. Hemolyzed erythrocytes appear to contain renin-activator and a vasoconstrictor as well, and for this reason hemolysis must be prevented (Table I).

DETERMINATION OF PERIPHERAL VASOCONSTRICTOR SUBSTANCE

It has been shown that plasma from patients with hypertension and from dogs with experimental hypertension causes marked vasoconstriction in the rabbit's ear when the ear is perfused with blood from dogs from which both kidneys have been removed eighteen or more hours before.[10] Blood from such animals we have called "arenal blood" for convenience.

Either plasma or serum may be employed for this assay (Table I). Hemolysis greatly increases their vasoconstrictor action, and hence must be avoided. Plasma which is free of hemolyzed cells and has been kept sterile in the refrigerator does not decrease in potency for at least four days.

The arenal blood used to perfuse the rabbit's ear may be drawn from the dog twelve to eighteen hours after nephrectomy (Table II). The results show that, even after marked retention of urinary excretory products has occurred, the blood is suitable for perfusion.

TABLE II

VASOCONSTRICTOR ACTION OF HYPERTENSIVE PLASMA WHEN INJECTED INTO PLASMA DRAWN AT VARIOUS INTERVALS AFTER NEPHRECTOMY

TIME AFTER NEPHRECTOMY BLOOD DRAWN FOR PERFUSION (DAYS)	AMOUNT OF PLASMA INJECTED (C.C.)	INITIAL FLOW PER MINUTE (DROPS)	DURATION OF REDUCTION OF FLOW (MIN.)	REDUCTION OF FLOW (%)	TIME AFTER BLOOD DRAWN FROM HYPERTENSIVE DOG* (B.P. = 170) (HOURS)
1	0.2	18	3.25	60	1
2	0.2	28	3	47	1
2	0.2	20	2.5	53	24
3	0.2	26	2.5	51	1
3	0.2	22	3	57	24
3	0.2	22	3	53	48
					From a normal dog after renin injection
1	0.2	16	3	58	1
2	0.2	22	3	50	24
3	0.2	24	3	44	48
					From a hypertensive* dog (B.P. = 190)
1	0.2	30	4.25	64	48
1	0.2	28	4.25	60	24
1	0.2	30	4.25	64	24

*Silk perinephritis method.

EVALUATION OF RESULTS

Samples of 0.2 c.c. of plasma, whether from normal or hypertensive patients or animals, when perfused with Ringer's solution, should not cause appreciable constriction, i.e., not greater than 25 per cent for two minutes. Renin alone should cause no constriction, but the mixture with plasma may elicit vasoconstriction of 60 to 80 per cent, lasting from three to six minutes.

When arenal blood is used as the perfusing medium, the injection of plasma from normotensive subjects should cause a maximum of 25 per cent constriction for two minutes. Usually the effect is less marked, i.e., a constriction of 15 per cent, lasting one minute. Plasma from hypertensive subjects causes a constriction of 40 to 70 per cent, lasting three to six minutes (Table III).

Since there is some variation in the results obtained on different ears, it is desirable to repeat the assay on at least two ears, and usually on the same ear twice. When the effects of various procedures are being tried on patients or animals, several determinations on different ears

suffice, for ordinarily there is not a great variation when the test is carried out skillfully. It is always desirable to control each series of determinations by the use of plasma from a normotensive subject.

TABLE III

TYPICAL EXAMPLE OF THE REPRODUCIBILITY OF THE VASOCONSTRICTION RESULTING FROM PERFUSION OF PLASMA (0.2 C.C.) OF A HYPERTENSIVE DOG (SILK PERINEPHRITIS) WITH ARENAL BLOOD ON 14 OCCASIONS

DATE	AV. MEAN B.P. (MM. HG)	REDUCTION OF FLOW IN			
		NORMOTENSIVE CONTROL		HYPERTENSIVE PLASMA	
		MIN.	%	MIN.	%
June 3	184	1.75	10	4.5	47
5	160	1	8	3.75	40
10	188	1.5	16	3	37
13	180	2	17	3.5	50
15	174	1.5	13	3	41
16	180	1	16	2.5	45
20	180	1	18	3.5	41
23	200	1	8	3	47
24	188	1.25	20	5.5	47
26	186	1	17	4	34
27	198	1.75	17	3.25	47
July 7	202	1	19	3	45
8	204	1.25	25	5	47

Tachyphylaxis After Repeated Perfusion of Angiotonin.—When Ringer's solution is employed to perfuse an ear, and angiotonin (0.2 c.c.) is injected, vasoconstriction results. The dose which is given directly after the initial drop rate has been resumed usually produces a much smaller constriction, and the third or fourth may elicit none at all. Ears vary considerably in this respect; some require as many as nine or more doses of angiotonin. The injection of a small amount (0.2 c.c.) of plasma, or the filtrate from boiled plasma, either mixed with angiotonin or given just before the angiotonin, restores the vasoactivity of the angiotonin. If, instead of administering plasma, a rest of forty-five minutes is allowed, full activity reappears.

When blood is substituted for the Ringer's solution, tachyphylaxis does not occur nearly so quickly, but does so eventually. A rest period of thirty to forty-five minutes restores reactivity (Table IV), but then tachyphylaxis develops readily when more angiotonin is administered.

It would seem reasonable to conclude from these experiments that the refractory state induced by repeated injections of angiotonin is due to exhaustion of some substance in the walls of the blood vessels, the precursor of which, or the substance itself, is contained in blood plasma. This is the substance we have conceived of as angiotonin-activator. It is our hypothesis that this substance, or its precursor, is in the blood vessel walls, because rest restores vasoconstrictor activity when angiotonin is injected, even though no source is available, i.e., when

Ringer's solution is used as the perfusion medium. That it must be incorporated into the protoplasm of the cells of the vessel walls is suggested by the fact that tachyphylaxis develops when injections of angiotonin are given repeatedly and in quick succession, even though blood—a source of activator—is immediately available.

TABLE IV

EFFECT OF REST PERIODS ON THE OCCURRENCE OF ANGIOTONIN TACHYPHYLAXIS

AMOUNT OF ANGIOTONIN (C.C.)	EAR PERFUSED WITH NORMAL DOG'S BLOOD		
	DROP RATE	LENGTH OF CONSTRICTION (MIN.)	REDUCTION OF FLOW (%)
0.5	29	5	69
0.5	17	6	83
0.5	16	5.5	58
0.5	10	6	42
0.5	17	7.25	57
0.6	11	7	59
Rest 45 min.			
0.5	11	8	73
0.5	9	3.75	37
0.5	9	0	0
Rest 30 min.			
0.5	14	7.5	67
0.5	10	0	0
Rest 30 min.			
0.5	13	6.5	50
0.5	13	1.5	27
0.5	9	0	0
Rest 30 min.			
3.0	13	5.5	47

Since refractoriness develops from repeated injections of angiotonin, it is important to avoid repeating them too frequently if reproducible results are to be expected. A rest period of ten to fifteen minutes usually suffices after the drop rate has returned to its initial value following vasoconstriction.

SUMMARY

A method for perfusing isolated organs, especially rabbits' ears, with blood or Ringer-Locke's solution, under pulsatile pressure, has been described. Its applications to the assay of blood samples containing renin, renin- and angiotonin-activator, and the angiotonin-like vasoconstrictor action of peripheral blood are recorded.

Tachyphylaxis to angiotonin in the rabbit's ear may be established by repeated, frequent injections, and the tachyphylaxis may be overcome by additions of either plasma or boiled plasma filtrate to the injected angiotonin, or by a rest period. It is suggested that angiotonin tachyphylaxis is in part due to exhaustion of a heat-stable substance, or its precursor, which is contained in plasma and is necessary for vasoconstriction. The cells in the wall of the blood vessel can either syn-

thesize this substance, or absorb the necessary constituents from Ringer's solution, for rest, while the ear is being perfused with Ringer's solution, abolishes tachyphylaxis.

I wish to express my sincere appreciation to Mrs. Marian Norman, John Tilden, and Mr. Clifford Wilson for their aid in this investigation.

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THE VALUE OF CARBON DIOXIDE BATHS IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASE AND ALLIED CONDITIONS

IRWIN D. STEIN, M.D., AND IRVINE WEINSTEIN, M.D.
NEW YORK, N. Y.

INTRODUCTION

FOR over half a century, carbon dioxide baths have been employed in the management of vascular disease. The dissolved gas, because of its solubility in both the watery and fatty constituents of the skin,[1-3] diffuses through the dermal layers, thus coming into intimate contact with the network of small blood vessels and causing them to dilate. The rationale for the use of carbon dioxide in cardiac and peripheral vascular diseases depends upon this specific vasodilating effect.[4, 5]

In order to convince ourselves of the claims which have been made in its behalf, investigations along related clinical and experimental lines were undertaken.

TECHNIQUE OF ADMINISTRATION

A concentration of 1 to 4 Gm. of carbon dioxide per liter of solution is essential for the production of the maximum therapeutic effect.[6] Natural springs, like those at Nauheim and St. Moritz, contain this optimum concentration, but in hospitals it is necessary to employ artificial methods involving either the introduction of already prepared gas into solution, or the introduction of chemical substances to form the gas in the bath. In the first instance, the gas is led from the tank to the bottom of the bath, where it is dispersed through the water from a wide-surfaced nozzle with multiple, fine apertures; in the latter method, which is the technique employed at Montefiore Hospital, measured amounts of acid and alkali are brought together, liberating carbon dioxide gas. The necessary quantities are readily calculated from the molecular weights. In practice, about 0.5 pound of ordinary commercial sodium bicarbonate and 200 c.c. of commercial hydrochloric acid in a total volume of 40 liters of water are used. There need be no fear of the presence of unneutralized acid with these proportions; as a matter of fact, there should still be a slight excess of alkali in the bath at the end of treatment.

Our experience has shown that the most suitable and inexpensive containers for the bath are water-tight wooden barrels* of 40-liter capacity. The barrel is filled with tap water at a temperature varying between 32° and 36° C., which is just comfortable for the extremities. Higher temperatures are not employed because they would exert a direct thermal effect on the limb and also retard the passage of the gas from the solution.

From the Physical Therapy Department and the Laboratories of the Medical Division, Montefiore Hospital, New York.

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*A pickle barrel, thoroughly cleaned, is admirably suited for this purpose.

The bicarbonate is thrown in and dissolved with a few swirls of the hand; the patient sits comfortably on a high stool or wheel chair and places his legs in the bath, immersing them to the knees. Ulcerations may be covered with a thin layer of vaseline in order to prevent direct contact with the solution, which sometimes causes pain. The acid is then siphoned* into the bath well below the surface of the water, so that the chemical reaction takes place near the bottom of the barrel. By introducing the acid slowly in this way, the evolution of gas is also slow, and the extremities are exposed in their entirety to fine bubbles of carbon dioxide gas. A turbulent reaction which comes to an end soon after mixing is not desirable.

At the end of one-half hour, the extremities are carefully dried and oiled, and then gentle massage may be instituted. As the legs emerge from the bath, the skin is reddened; the color varies from a pale rose to a bright pink. The skin is slightly warm, although the bath itself is of an indifferent temperature. There is a sharp line of demarcation corresponding to the level to which the limbs are immersed. Other effects often noted are disappearance of the shiny glaze of atrophic skin, as well as an increase in softness and elasticity of the skin itself, and an increase in the firmness of the subcutaneous tissue. These changes are most marked after several weeks of treatment and are due, in part, to the better nourishment of the skin and, in part, to massage or other concomitantly used physical measures. The hyperemia usually disappears shortly after removal from the bath but may persist for one-half hour or longer. The immediate subjective results from one bath are not very striking, but, after a course of daily treatment lasting from one to two weeks, the pain of ischemia, whether at rest or on motion, is often diminished or has disappeared. The treatments may be repeated several times each day. In fact, the patient may be taught to administer the baths himself at home, after the danger of using acid solutions has been explained. No expensive or complicated and cumbersome machines are required for its administration, and many individual treatments can be given in a busy department with a minimum of effort.†

CLINICAL INVESTIGATIONS

The following procedures were carried out on representative groups of patients, some with normal peripheral vessels and others with varying degrees of peripheral vascular disease.

Capillary Microscopy.—The skin of treated regions in the extremities of thirty patients was examined directly with the aid of the capillary microscope. The most striking change was the extraordinarily large number of capillary tufts and loops which had become visible; there were many more than had been seen in the same area before exposure to carbon dioxide. In addition, the lumina of both the arterial and venous limbs of the capillaries were larger and contained blood which was brighter in color (presumably better oxygenated) than prior to treatment (Fig. 1). The blood flow in many of the capillaries was distinctly accelerated, so that the granular appearance of slowly cir-

*Commercial hydrochloric acid is diluted three times with tap water and stored in the large, brown gallon bottle in which this acid originally comes. A simple siphon arrangement of glass and rubber tubing facilitates handling. Since about 600 c.c. of the diluted acid are used per treatment, the storage bottle may be marked off appropriately to give enough acid for six or seven treatments.

†An indication of the popularity of this mode of treating vascular disease of the extremities at the Montefiore Hospital is readily seen from the statistics. In 1940, approximately 4,000 hydrotherapeutic treatments were given in the physical therapy department. Of these, almost 1,500 were carbon dioxide baths.

culating blood, when individual corpuscular elements can be discerned, was lost. The flow in the larger tributaries, the so-called "venous sinuses" which are situated more deeply in the skin, was also speeded up. The treatment hastens the emptying of their slow-moving cyanotic blood and contributes to the more efficient delivery of arterial blood to the tissues. The changes just described are characteristic of active hyperemia.

Although with this method of clinical observation only superficial vessels are clearly visualized, the increased redness of the background indicates that deeper vessels in the subpapillary plexuses and in the subcutaneous tissues are probably also involved in the reaction. This corroborates the observations of Hirsch[7] and Benatt and Honighaus.[8] Most investigators feel that the vasodilatation is due to a direct chemical influence upon the muscle elements of the vessel walls; however, the possibility that it may be the result, in whole or in part, of a vascular axon reflex must also be borne in mind.

Skin Temperature.—In general, it may be said that with active hyperemia and an increase in blood flow a rise of local temperature occurs. For this reason, the skin temperature of treated extremities was observed and charted by means of a thermocouple and galvanometer. Eleven patients form the basis of these observations; nine had peripheral vascular disease of the arteriosclerotic type, and two served as normal controls. Inasmuch as the results were approximately the same in all cases, only one will be presented in detail (Fig. 2). In each instance, control readings were taken at the same area under the basal experimental conditions, i.e., room temperature, time of day, period of rest, etc., but with tap water instead of the carbon dioxide bath.

Regardless of the nature of the bath, whether tap water or carbon dioxide, there is a sharp rise in the skin temperature of the toe shortly after immersion; this rise approximates closely the temperature of the bath. As soon as the limbs are withdrawn there is a sharp fall in skin temperature; this is most marked during the first five minutes. After the initial drop, the fall is more gradual, and, in the case of the carbon dioxide treated extremity, it is usually from one-half to one and one-half hours before the skin temperature of the toe returns to its basic resting level. When tap water is used under similar conditions, this resting level is reached in a much shorter time, usually from five to twenty minutes after removal from the bath.

The maintenance of a few degrees (1° to 3°) of temperature elevation for one-half to one and one-half hours does not appear to be startling evidence of the effectiveness of carbon dioxide. It must be remembered, however, that under normal conditions the exchange of heat between the skin and surrounding air is quite rapid, and is a manifestation of the temperature-regulating function of that organ. This is especially

true of the distal areas, such as the finger tip or the base of the toes, where there are unusually large numbers of arteriovenous anastomoses. Even when extremities are exposed to prolonged heating, the surface temperature falls rapidly once the source of the heat is removed. The persistence of a mild temperature rise for a variable period after exposure to carbon dioxide assumes a greater significance in the light of these facts. In all probability it means that the vasodilating factor remains present and active in the tissues for an appreciable length of time.

Fig. 14.—Capillaries of the nail fold before treatment with carbon dioxide. Photomicrograph from the finger of Mrs. F. N., aged 43 years, who had mild vascular disease of the lower extremities, but whose upper extremities were clinically normal.

Plethysmography.—As a result of vasodilatation, there is an increase in limb volume. The increase represents the additional amount of circulating blood present in the vascular channels, and an additional store of nutritive substance for tissue use. Although such studies have been employed in the past,[9] they were undertaken again with the hope that they might furnish a quantitative measure of the effectiveness of carbon dioxide.

Portions of the lower extremity approximately 10 inches in length, including the bulk of the calf muscles, were enclosed in a water-tight

plethysmograph of the type used by Lewis and Grant[10] and adapted for use on the leg. Each limb segment was kept in contact for one-half hour with a carbon dioxide bath generated in the plethysmograph. At the end of this period, the bath was rapidly siphoned off and replaced immediately by tap water of the same temperature. Blood inflow curves were taken before and after the development of the skin hyperemia, using the well-known method of Hewlett and Van Zwaluwenberg.[11]

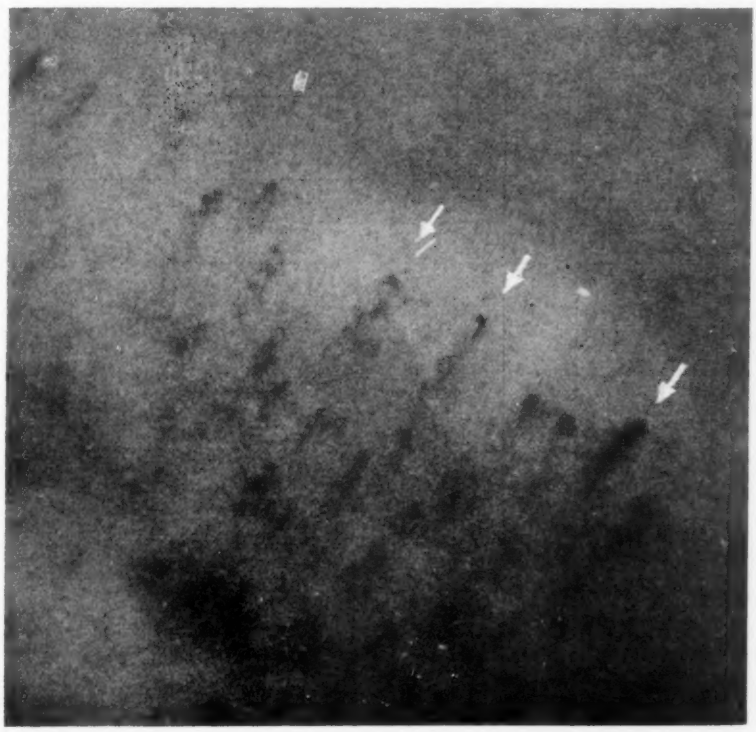

Fig. 1*B*.—Capillaries of the nail fold after exposure to a carbon dioxide bath for one-half hour. Notice the increase in the number of capillaries as well as the dilatation of these vessels (arrows). Photomicrograph from the finger of Mrs. F. N.

A collecting pressure of 40 to 70 mm. Hg* was thrown into the cuff proximal to the plethysmograph. As early investigators[11] have shown, when the venous circulation is suddenly occluded by a pressure of this magnitude, which, of course, does not impede arterial flow, the increase in limb volume can be considered as the arterial inflow. Certain technical precautions[10] must be heeded, however, if reliance is to be placed on the results. The inflow can be registered graphically, and, since the area of the limb segment enclosed is readily ascertained, the amount of blood flow per unit of time per 100 c.c. of tissue is therefore known.

*The pressure used was the one which gave the optimal blood inflow in the control curve.

TABLE I

CASE	NAME	AGE (YR.)	SEX	DIAGNOSIS	CLINICAL FEATURES	BLOOD INFLOW (C.C./100 C.C. TISSUE PER MIN.)		COMMENT
						CONTROL	CO_2	
1	H. K.	30	F	Ulcerative colitis	Extremities normal	2.3	5.7	About 150% increase in blood flow maintained for 30 min. after CO_2 bath
2	D. T.	22	M	Multiple sclerosis	Extremities normal	2.0	3.2	Approximately 60% increase in blood flow
3	G. W.	23	M	Multiple sclerosis	Extremities normal	4.6	5.3	Approximately 15% increase in blood flow
4	H. J.	42	M	Parathyroid disease	Extremities normal	2.6 2.2	3.9 3.7	Approximately 55% to 70% increase in blood flow
5	S. M.	47	M	Portal cirrhosis	Extremities normal	2.0	2.0	No change in blood inflow after treatment. Although the patient's peripheral circulation appeared grossly normal, it may be that his lack of response was due to the inhibiting effect of hepatic toxins on his smaller blood vessels
6	S. R.	46	M	Raynaud's syndrome	Spontaneous amputation of several fingers and toes in the past; pale and cold hands and feet which become a slate-blue during cold weather; all peripheral arteries patent; good collateral circulation	1.8	3.1	Approximately 70% increase in blood flow

7	L. A.	60	M	Scleroderma	Typical leathery appearance of skin, associated with tightness which was most marked over joints	0.42	0.91	Good response to CO_2, with approximately 100% increase in blood flow. The low absolute values were probably due to inability to increase limb volume because of tightness and inelasticity of skin
8	M. Ku.	55	M	Arteriosclerotic peripheral vascular disease; pulmonary tuberculosis	Only femoral and popliteal vessels patent; good collateral circulation	2.8	5.5	Approximately 100% increase in blood flow
9	E. H.	66	F	Peripheral vascular disease; arteriosclerosis; diabetes; peripheral neuritis	Only right femoral artery patent; good collateral circulation	2.2	4.3	Approximately 100% increase in blood flow
10	J. Y.	68	M	Peripheral vascular disease; arteriosclerosis; diabetes	Femoral artery patent; fair collateral circulation	3.2	5.4	Approximately 70% increase in blood flow
11	J. S.	68	M	Peripheral vascular disease; arteriosclerosis	Left femoral artery patent; cold skin and livid cyanosis of feet	1.1	2.0	Approximately 100% increase in blood flow
12	D. B.	70	F	Peripheral vascular disease; arteriosclerosis; diabetes	Femoral and popliteal vessels patent	2.9	3.7	Approximately 25% increase in blood flow
13	B. F.	54	F	Peripheral vascular disease; arteriosclerosis; diabetes	Femorals and right popliteal vessels patent	0.99	1.4	Approximately 40% increase in blood flow
14	J. W.	50	F	Peripheral vascular disease; arteriosclerosis; diabetes	Only femoral and popliteal vessels patent	4.9	5.5	Approximately 15% increase in blood flow
15	M. Ke.	63	M	Peripheral vascular disease; arteriosclerosis	Only femoral and popliteal vessels patent	2.9	6.3	Approximately 125% increase in blood flow

Such procedures were carried out on extremities which were the seat of peripheral vascular disease, as well as on normal controls (Table I). In general, it may be said that, if a limb becomes hyperemic when exposed to carbon dioxide, there will be, at the same time, an increase in blood flow. This is best seen in the graphic representations (Fig. 3*A* and *B*).

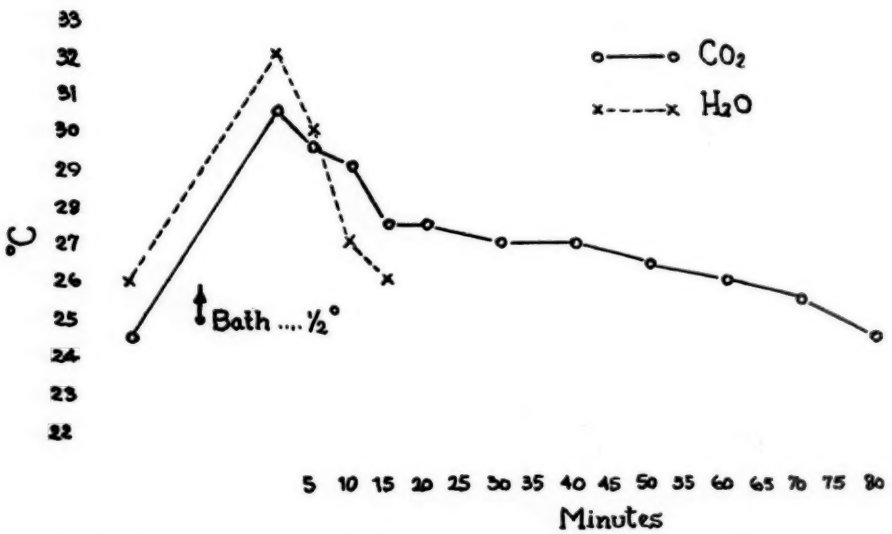

Fig. 2.—Skin temperature of the left great toe. The patient was the same woman whose capillaries are pictured in Fig. 1. The rapid return of the skin temperature to normal shortly after removal from the control bath of tap water and the maintenance of the temperature rise following the carbon dioxide bath are well illustrated. Slight differences in the initial temperature levels of the great toe are physiologic and are to be expected, inasmuch as the test baths were carried out on consecutive days.

Values of 2 to 4 c.c. of blood flow per 100 c.c. of tissue substance per minute are normal for the extremities when flow is estimated by the plethysmographic method.[11] It would seem that these values should be much lower when varying degrees of obliteration of the vascular bed have taken place. That this was not so in most of the peripheral vascular disease cases which we studied is evident from Table I; the inflow figures are well within the normal range. To anyone who can picture the rich collateral circulation which develops in response to the stimulus of tissue anoxemia, this need not come as a surprise. In a previous paper[12] we have shown that simple ligation of the main vessels of the rabbit's ear results in the development and widespread ramification of the smaller caliber vessels in that ear in a relatively short time. Allen and Camp[13] have shown by means of arteriographic studies that the same process occurs in the human being. Indeed, in an occasional case, the channels may be so well developed that the rate of blood flow to the tissues may be well above normal (Table I, Case 14).

In the few instances in which the inflow rates were low (Table I, Cases 11 and 13), the degree of vascular change, when measured by the usual clinical methods, was so extensive as to indicate very little

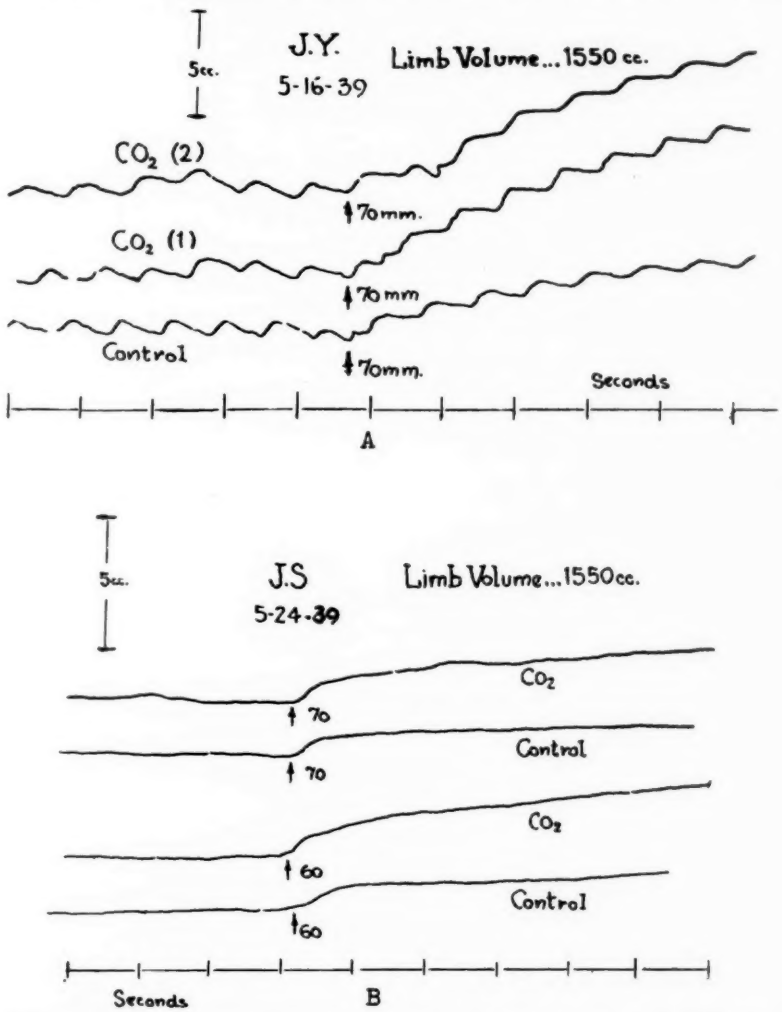

Fig. 3.—Inflow curves (plethysmograms) from the leg. *A*, Case 10 (Table I). A comparison of the lowest or control curve (water bath) with the two upper curves (after exposure to carbon dioxide in the plethysmograph for one-half hour) shows an increase in blood inflow of 70 per cent, a rise of from 3.2 c.c. blood per 100 c.c. tissue volume per minute to 5.4 c.c. per 100 c.c. per minute. The arrow and the number adjacent indicate the point at which 70 mm. Hg pressure was placed on the extremity. Note that individual pulse waves are present in this graph. *B*, Case 11 (Table I). In this patient the disease process was so advanced that there was only a "nonpulsating" circulation in the legs. This is confirmed by the absence of pulse waves in the graph. Despite this, a comparison of the inflow curves shows an increase of blood flow after the carbon dioxide bath. This approximates 100 per cent (1.1 c.c. blood inflow to 2.0 c.c.).

reserve. No pulse wave was visible in the plethysmographic curve obtained from such patients. In their extremities, the metabolic demands must be supplied by "nonpulsating circulation" of small, fine caliber

vessels, and by pathologically patent arteriovenous anastomoses. Neither group of vessels is capable of supplying large amounts of blood directly to the tissues under times of stress.[14] The peripheral circulation under such conditions cannot be described in terms of blood flow, but more properly as a sort of "seepage."

In any event, regardless of the absolute values for blood flow, or the nature and extent of the underlying pathologic process, there was an increase in blood flow of 15 per cent to 150 per cent in the extremity treated with carbon dioxide. This increase must obviously be a beneficial influence; it means better tissue nourishment, as well as more adequate removal of tissue metabolites.

Although the blood flow is moderately increased in most cases, in all probability the increase is due to an effect primarily on the skin and other superficial vessels. This is in sharp contrast to the work of earlier investigators,[4, 16] who maintained that there was a profound effect on the deeper and larger caliber vessels. There can be little question that, if such were the case, the increase in blood flow would of necessity be of far greater magnitude.

DISCUSSION

The increasing interest in chronic disease has driven home one salient point—the danger of so-called "vigorous treatment." It is a matter of common knowledge that an organ which is no longer young and elastic cannot accommodate itself readily to extreme changes as well as a perfectly functioning unit. Thus, intensive antisyphilitic therapy may cause irreparable damage in an otherwise symptomless case of tertiary syphilis; or repeated and profound diuresis may cause an ailing heart and overworked kidneys to go further into failure.

In organic peripheral vascular disease, which is the chronic disease par excellence, this is doubly true. Measures designed to produce vasodilatation or to stimulate the formation of collateral channels may defeat their very purpose by increasing the metabolism of the tissues to such an extent that it is impossible to satisfy their needs, even if all of the vessels available were in use. An increase in pain may ensue, and the possibility of tissue death and necrosis is enhanced. It is for this reason that such measures as local heating, shock therapy, and hyperpyrexia, although still widely used, have fallen into disrepute in the treatment of the elderly patient or of patients with extensive vascular disease. These modalities are not for everyday use; they belong in the realm of him who is trained in the treatment of peripheral vascular disease.

In carbon dioxide we have a therapeutic agent which produces vasodilatation and increased blood flow without increasing tissue metabolism

or the work of the heart and other vital organs.* The usual ambulatory patient, perhaps a man 50 to 60 years old, who has mild diabetes and a history of cramps in the calves of both legs, with consequent disability, who shows feeble or absent pulsations and oscillometric readings, and has a fairly good compensatory circulation, as revealed by clinical tests, may derive much benefit from treatment with carbon dioxide baths. Such treatment does not cure the underlying disease, of course, but it frequently relieves the signs of circulatory insufficiency, i.e., pain, rubor, cyanosis, and atrophy of the skin.

It is not a cure-all for vascular disease of the extremities. Other forms of therapy may prove more efficient in a given case, and patients may fail to respond favorably to carbon dioxide in spite of a bright red hyperemia of the skin. If carbon dioxide is used primarily with the intention of developing and maintaining collateral circulation, it is a welcome addition to our armamentarium. There are also contraindications to its use, of course. Deep, open wounds, purulent infections, and dry gangrenous processes are chief among these.

Clinical studies indicate that carbon dioxide has a definite surface effect, and, in all probability, some action on deeper structures, also. A priori, it would appear that its use would be of value in several conditions which are commonly included in the realm of peripheral vascular disease.

First and foremost are the superficial ulcerations and necroses which are so frequently caused by local arteriolar closure (arterioles and small arterial branches) or varicose veins. These lesions vary in extent but commonly involve only several layers of the skin, possibly with the superficial portion of subcutaneous tissue. We have been agreeably surprised in many cases, in some of which the lesions were refractory to the more generally used methods of treatment, by the prompt healing which took place.

It has also been used in vasospastic conditions, such as the group of disorders comprising the so-called Raynaud's syndrome, as well as in generalized arterial disease of undetermined etiology and thromboangiitis obliterans. With the removal or counterbalancing of the spasm, subjective and objective improvement has followed. In these conditions, as well as in others, carbon dioxide is only an alternative type of treatment; there are other methods which may be more effective.

In vasoparetic disorders, such as acrocyanosis and erythromelalgia, its use may also produce surprisingly good results.

Finally, it has been employed in several cases of scleroderma. Inasmuch as the diseases seen in a hospital for chronic disease are, without

*These remarks concern the action of carbon dioxide upon the extremities. When the entire body is immersed in a carbon dioxide bath, various mechanical, thermic, and reflex factors must be considered. For the sake of brevity they have not been included in this paper, but they are described in detail in an article by Harpuder[6] on experimental balneotherapy.

exception, of extremely long standing, little more than subjective relief could be expected. All of these patients had the typical mummification of the skin, as well as sclerodactylia. It is our belief that, early in the disease, there might be a synergistic action between a method of general treatment, such as the carbon dioxide body bath, and the local application of histamine or mecholyl iontophoresis,[15] which would heighten the benefits to be obtained.

SUMMARY AND CONCLUSION

Carbon dioxide, by virtue of its chemical properties, is capable of producing active hyperemia when in intimate contact with the body surface. This hyperemia is localized to the area treated and is unaccompanied by an appreciable rise in tissue or general metabolism. The carbon dioxide bath does cause an increase of blood flow, which, we assume, is chiefly in the superficial layers of the subcutaneous tissue and the skin. No proof can be given at this time of deeper penetration or action. As a result of this increase in blood flow, the bath is a gentle and effective method of treating a selected group of patients who, in general, are elderly persons with diffuse, far-advanced disease, but have a fairly good collateral circulation in spite of pain, skin and color changes, and occasional superficial necroses. The carbon dioxide bath is a palliative method of treatment which aids in preserving the peripheral circulation by releasing spasm and aiding in the production of compensatory circulation, and by not increasing tissue metabolism.

The use of the carbon dioxide bath is also suggested in refractory cases of superficial necrosis, vasospastic disease, and scleroderma.

We wish to express our thanks to Dr. Karl Harpuder, Attending Physical Therapist at the Montefiore Hospital, for his advice and encouragement during the course of these experiments.

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CENTRAL NERVOUS SYSTEM MANIFESTATIONS IN ACUTE MYOCARDIAL INFARCTION

WILLIAM BENNETT BEAN, M.D., AND CHARLES THOMAS READ, M.D.
CINCINNATI, OHIO

RECOGNITION of the clinical characteristics of acute coronary artery thrombosis, with cardiac infarction, has become commonplace since the pioneer work of Herrick.[1] Pain, the most alarming aspect of such seizures, has been emphasized in dramatic language.[1-4] In spite of recent emphasis on the fact that the attacks may be painless, an important reason for overlooking an acute attack is the absence of pain as a major symptom.[5-7] On the other hand, pain in the chest is likely to lead to a diagnosis of cardiac infarction without critical exclusion of other possible causes.[5, 6] Because of the many obstacles in the way of correct interpretation of atypical cases of infarction of the heart we have undertaken a retrospective study of autopsy material. This paper presents a group of cases in which the symptoms indicated acute cerebral disease, but autopsy revealed a recent myocardial infarct and no *acute* cerebral vascular lesion.

MATERIAL AND METHODS

We have examined the autopsy protocols of all cases of myocardial infarction found in the department of pathology of the University of Cincinnati Medical School for the twenty years ending with 1940 (Table I). The records include material from the pediatric service, and from the Chronic Disease Hospital since 1930. These are the routine autopsy records, compiled by the senior and junior pathologists under the direction of Dr. Richard S. Austin. The criteria for the diagnosis were the same as those used by one of us in a previous study.[7] Doubtful cases were discarded.

In seven* of the eight cases an acute vascular lesion in the brain was diagnosed because of the neurological symptoms. In only two was an infarct of the heart suspected. In order to establish criteria to exclude the possibility of acute cerebral vascular lesions, it would be desirable to have injection or meticulous dissection of the entire arterial tree of the brain, and multiple sections of certain areas. Such desiderata were not possible in these cases. Since the clinical diagnosis pointed to an acute cerebral vascular lesion, the pathologist was on the lookout for embolus, thrombus, or hemorrhage. It seems improbable that any extensive lesion was missed. Our cases satisfy these criteria: (1) The presenting symptoms were interpreted as arising from an acute cerebral vascular lesion or intracranial disturbance. (2) Arteriosclerosis of the cerebral arteries was advanced (except in Case 4). (3) No hemorrhage, embolus, or thrombus was found in the brain. (4) An infarct of the heart was found. The age of the infarct made it probable that it occurred at the time of the cerebral symptoms.

From the Departments of Internal Medicine and Pathology of the College of Medicine of the University of Cincinnati, and the Cincinnati General Hospital.

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*The eighth case was that of an epileptic.

In the entire series we found eight other cases of recent cardiac infarction, with similar symptoms and clinical diagnosis. They were discarded because the brain had not been examined. In seven instances, unrecognized cardiac infarction occurred in patients with long-standing hemiplegia. In nine, hemiplegia followed cardiac infarction, but in only three was it reasonably certain that a mural thrombus had contributed an embolus. In four additional cases of cerebral and coronary thrombosis it could not be ascertained which came first, or whether they were related.

TABLE I

INCIDENCE OF MYOCARDIAL INFARCTION

YEAR	TOTAL AUTOPSIES	MYOCARDIAL INFARCTS	PERCENTAGE
1921	261	0	0.0
1922	249	3	1.2
1923	300	2	0.7
1924	281	2	0.7
1925	306	3	1.0
1926	422	3	0.7
1927	483	13	2.7
1928	553	16	2.9
1929	664	13	2.0
1930	652	21	3.2
1931	601	23	3.8
1932	754	32	4.2
1933	778	43	5.5
1934	887	40	4.5
1935	762	29	3.8
1936	981	65	6.6
1937	1003	61	6.1
1938	818	44	5.4
1939	715	53	7.4
1940	724	46	6.4
	12,194	512*	4.2

*White males, 305; colored males, 84; white females, 83; colored females, 40.

Several cases in which there were similar neurological signs and symptoms were found in other forms of heart disease. Most of these were in association with advanced coronary and cerebral arteriosclerosis, and usually with hypertension. In one instance, diffuse interstitial myocarditis (Feidler's) was found. It was suspected, but could not be proved, that these attacks were associated with a sudden fall in blood pressure.

REVIEW OF THE LITERATURE

If we omit Hammar's interesting case of coronary embolism with extreme bradycardia and syncope,[8] Huber[9] was the first to stress cerebral manifestations in coronary thrombosis. This made no impression upon the minds of clinicians at that time because it was believed universally that such an event as coronary obstruction was necessarily fatal. Errors of omission in the diagnosis of cardiac infarction have become possible only since the widespread dissemination of knowledge of the usual symptoms of an acute attack. Although in his first paper Herrick[1] remarked that "the mind is nearly always clear," he mentioned cases in which there were mental apathy and marked general weakness.

Similar cases have been observed frequently.[2, 3] White[4] mentioned weakness in older people, and "mental disturbances, faintness, dizziness and even syncope with coma and convulsions. . . . Prolonged coma lasting for hours or even days, especially in aged persons, may rarely follow the temporary or prolonged drop in blood pressure that sometimes accompanies acute coronary thrombosis."

The nature of focal cerebral vascular lesions which follow acute infarction of the heart is not simple, as is often assumed. Hemiplegia after such an attack may arise in at least three ways. The mechanism usually invoked is embolism from a dislodged mural thrombus. Master, Dack, and Jaffe[10] have shown that this is particularly serious in the younger patients. In a series of 300 autopsy cases, one of us[11] found that, of fifteen adequately studied cases in which hemiplegia followed an acute myocardial infarct, only six were embolic in nature. Nine resulted from a local vascular fault; seven of these patients had thrombi, and two had hemorrhages. It is probable that low arterial blood pressure and reduced cerebral blood flow favored thrombus formation. Why hemorrhages should have occurred is obscure.

The time of occurrence of hemiplegia after infarction of the heart is of some help in differentiating thrombosis from embolism. Changes in circulatory dynamics appear soon after damage to the heart. If hemiplegia appears early, it is likely to have been caused by a thrombus or, if transient, by a reduction in effective cerebral circulation. Embolism from dislodged mural clots rarely occurs until after the first week.[11] Dozzi[12] has studied cerebral vascular sequels of coronary thrombosis. Twelve of his forty-one patients had hemiplegia, either thrombotic or embolic, which so masked the picture that the heart lesion was not appreciated. In the other cases the diagnosis was made ante mortem. He did not report the time relationships of the two lesions.

In their comprehensive monograph on carotid sinus syncope, Ferris, Capps, and Weiss[13] clarified at least three possible mechanisms—pulse slowing, fall in arterial tension, and a direct cerebral reflex. Mechanisms similar to the second or third of these might also explain cerebral disturbances after cardiac infarction, with or without a sensitive carotid sinus. If the circulation in the brain is considerably reduced, the resulting symptoms may so distort the clinical picture that the heart is completely overshadowed by focal or general central nervous system manifestations.

In this connection it is well to recall that there is evidence of cerebral disturbances in association with well-recognized abnormalities of cardiac function. The cerebral complications of bradycardia with the Adams-Stokes syndrome are well known.[14] Cerebral symptoms as a result of attacks of tachycardia were recorded as early as 1889 by Bouvert, according to Esmein and Donzelot.[15] In their paper on the syncopal

form of paroxysmal tachycardia, they reported cases in which a variety of cerebral symptoms were repeated regularly with each attack. They did not observe hemiplegia.

Blackford and Willius[16] described two cases of auricular flutter in which collapse occurred after a period of rapid ventricular activity. Barnes[17] made a special study of the cerebral manifestations of paroxysmal tachycardia. In fifteen of 104 cases there were severe symptoms, such as vertigo, blurred vision, and dizziness. In prolonged attacks these were very severe, and syncope, epileptiform seizures, blindness, and convulsions occurred. The symptoms were particularly severe in patients with cerebral arteriosclerosis.

Another group with central nervous system symptoms caused by cardiac dysfunction was reported by Dumas.[18] He observed a number of hypertensive patients who developed transitory hemiplegia during attacks of left ventricular failure and pulmonary edema. This occurred only when the arterial blood pressure fell during the attack. If the pressure returned to normal, the symptoms disappeared. In those who died, the most striking abnormalities were pulmonary edema and cerebral arteriosclerosis without thrombosis. The hemiplegia was explained as the result of ischemia which made itself felt particularly in areas whose blood supply was already impaired by arterial lesions.

A group with similar symptoms was reported by Fleming and Naffziger.[19] Their patients developed temporary hemiplegia after sudden decreases in arterial blood pressure or a sudden change in position. When they were given adrenalin or other stimulants, the hemiplegia disappeared pari passu with the restoration of arterial tension. All of these patients had sclerosis of the cerebral arteries. It was concluded that any precipitous fall in arterial blood pressure, such as that associated with myocardial weakness, surgical shock, or dilatation of the splanchnic vessels, could produce such symptoms whenever cerebral circulation was reduced.

The cerebral complications of various surgical operations have recently been studied by Behrend and Riggs.[20] These authors encountered coma, convulsions, focal cerebral symptoms, hyperpyrexia, and psychic disturbances. All of their patients had low arterial blood pressure and varying degrees of shock. No thrombi, emboli, or hemorrhages were discovered in the brains which they examined.

Thomas[21] described a patient with postural hypotension who had recurrent attacks of transient hemiplegia during periods of low or falling arterial blood pressure. These attacks could be reproduced at will by elevating the patient on a tilting table to 75° above the horizontal. Thomas believed "this apoplexy is caused by a fleeting localized cerebral ischemia which occurs in the course of a drop in blood pressure from postural hypotension. The degree of narrowing of the lumen

from arteriosclerosis of the various cerebral vessels determines the point at which ischemia first produces symptoms.''

From the foregoing observations it is clear that a form of hemiplegia may occur in persons with cerebral arteriosclerosis when there is a precipitous or extreme fall in arterial tension. The location and extent of the arterial lesions determine the focal signs and symptoms. Their severity will be influenced by the rate of fall and the duration of the hypotension. The permanence of focal signs will depend on these factors and the resulting damage to the brain. Although spasm of cerebral vessels might produce similar effects, it does not seem likely in sclerotic vessels.

We have been able to find only one study of the cerebral symptoms of acute myocardial infarction. Kjaergaard[22] reported three cases in which extreme collapse, confusion, coma, epileptiform convulsions, incontinence, and restlessness were the most conspicuous symptoms. At autopsy, acute infarcts of the heart were found. Unfortunately, in two cases the brain was not examined, so that the possibility of embolism, thrombosis, or hemorrhage cannot be excluded. In the third case the patient had fallen, and autopsy revealed a traumatic hemorrhage in the occipital region. Dozzi[23] has studied cases in which unsuspected coronary thrombosis was discovered at autopsy when the clinical picture was that of hemiplegia. There were infarcts or hemorrhages in the brain which were sufficient to account for the neurological changes. Fetterman and Ashe[24] have emphasized the ''cerebral debut'' which occurs in certain cases of heart disease. Although their report dealt primarily with patients with subacute bacterial endocarditis, they included one case of myocardial infarction. The patient had a reaction closely simulating delirium tremens. They believed that his bizarre symptoms depended upon cerebral anoxemia. At autopsy, ischemic changes were found in the brain. Abbott and Fay[25] reported a case of syncope and head injury. At autopsy coronary occlusion was found, without evidence of a cerebral lesion, and presumably with normal cerebral vessels. Here it is clearly impossible to exculpate many of the usual causes of syncope.[14] We have reported a somewhat similar case, in which it was suspected that the shock associated with a head injury was the precipitating cause of coronary thrombosis.[26]

Many patients with coma are neglected until after the early clinical patterns of their disease have been obliterated. When such patients are admitted to large general hospitals, the history is often wanting or imperfect. Careful physical examination is precarious. Soloman and Aring,[27] in an analysis of patients admitted to the Boston City Hospital, with coma as the conspicuous presenting symptom, found that cardiac disorders were responsible for 3.5 per cent of the nonalcoholic cases. Five of seventeen were later found to have coronary thrombosis, but no report of the status of the brain and its arteries was included.

From this observation it appears that coma, rather than cerebral symptoms with localizing signs, may herald the advent of cardiac infarction. Certainly, when it appears as a sequel it may obscure the main disorder.[4]

CASE REPORTS

CASE 1.—C. R. (Unit 118100), an 83-year-old white man, was admitted to the psychiatric service April 14, 1939, because of profound disorientation. This followed a period of increasing confusion which had begun six weeks before with left-sided paralysis. No other history could be obtained.

Physical Examination.—The temperature was 100.5° F.; the pulse rate, 100; and the respiratory rate, 24. The patient had Cheyne-Stokes' breathing. His blood pressure measured 130/80. He was a swearing, grimacing old man, dehydrated, cyanotic, and completely disoriented. Ophthalmoscopic examination revealed some blurring of the discs and tortuous, narrow arteries. There was dullness at the base of the right lung posteriorly, and moist râles were heard at both bases. Marked peripheral arteriosclerosis was noted. The heart seemed large but could not be percussed accurately because of the emphysematous chest. The impulse was 11.5 cm. from the midline. The heart sounds were very distant, but regular. No murmurs were heard, and there was no gallop or friction rub. There was constant rhythmical twitching of the right leg. Complete flaccid paralysis of the left arm was noted. Neurological examination revealed that the biceps, triceps, radial, and patellar reflexes were 2+ on both sides (0, absent; 4+, maximal). Both ankle jerks were absent. The Babinski, Oppenheim, and Chaddock reflexes were present on the right, as was a questionable Gordon's reflex. The abdominal reflexes could not be elicited. Pain sensation was present. The neck was not stiff. Lumbar puncture revealed an initial pressure of 5 cm. of water, with normal dynamics and cerebrospinal fluid.

Admission Laboratory Studies.—The erythrocyte count was 5,220,000; the leucocyte count, 27,000; and the hemoglobin, 13.6 Gm. per 100 c.c. The urine was normal except for a few leucocytes in the sediment.

Course in Hospital.—He remained disoriented, gradually became worse, and died ten days after admission. The diagnosis was thrombosis of the left middle cerebral artery, generalized arteriosclerosis, and bronchopneumonia. (Autopsy observations in all cases are found in Table II.)

CASE 2.—J. H. (Unit 33722), a 63-year-old white man, was admitted to the receiving ward at 1:30 A.M., Jan. 2, 1935, in a state of deep coma. It was ascertained that he had been treated for heart trouble in the past. About five hours before admission he had complained of a sudden pain, and he rapidly became unconscious. There were no convulsions or twitchings. When first seen, he was in shock. There was some frothing at the mouth. All deep reflexes were hyperactive and equal bilaterally. The pupils reacted to light. Ankle clonus was present bilaterally. The cremasteric and abdominal reflexes were absent. There was no focal weakness. He died suddenly while on the way to the ward. Nothing else was recorded. The diagnosis was probable cerebral accident, with cardiac insufficiency.

CASE 3.—H. B. (Unit 78524), a 61-year-old white man, was admitted to the medical service July 15, 1937, complaining of severe dyspnea, pain in the legs, and inability to use his left arm. Three years previously he had noticed numbness and severe pain in both legs on standing. A year later he began having attacks of nonradiating retrosternal pain after exertion, which was relieved by rest and never lasted over three minutes. Dyspnea on effort began soon after the first anginal

TABLE

CASE	AGE (YEARS)	SEX	RACE	HEART								
				WEIGHT (GM.)	CORONARY ARTERIES				INFARCTS		MURAL THROMBUS	
					ARTERIOSCLEROSIS	L. A. D.	CIRCUMFLEX	RIGHT	HEALED	RECENT	AURICLE	
											R	L
1 U-118100	83	M	W	550	++++ with ulceration and thrombus	Fresh thrombus	Narrow	Narrow	Apex of left ventricle	Apex of left ventricle around old infarct	0	0
2 U-33722	63	M	W	550	++++	Thrombus at origin	Marked A. S.	Thrombus at origin	Posterior and basilar in left ventricle	Anterior apical in left ventricle and septum	Small	Small
3 U-78524	61	M	W	475	++++ with calcification	Narrow; no thrombus	Narrow; no thrombus	Narrow; no thrombus	Anterior of left ventricle	Anterior and apex of left ventricle around old scar	0	Small adherent
4 U-67496	44	M	W	450	+++	Complete occlusion	Narrow	Narrow	Posterior and basilar in left ventricle and septum	Anterior and apical in left ventricle	0	0
5 U-89077	87	M	C	500	++++	Fresh thrombus	Old occlusion	Narrow	Anterior and apex of left ventricle; posterior and basal in left ventricle	Anterior and apical in left ventricle; large around old scar	0	0
6 U-106527	61	M	C	665	+++	Sclerotic	Narrow	Fresh thrombus; new origin	0	Posterior and basal in left ventricle	0	Small
7 U-104989	53	M	C	850	++++	All arteries very narrow; no thrombus	All arteries very narrow; no thrombus	All arteries very narrow; no thrombus	0	Posterior and basal in left ventricle	0	0
8 U-49873	45	M	C	375	++++ with much calcification	Thrombus at origin	Narrow	Old occlusion	Posterior and basal in left ventricle	Anterior and apical in left ventricle	0	0

L. A. D., Left anterior descending.

attack. For a year prior to admission he had had attacks of paroxysmal dyspnea. Nine days before admission he had a severe, prolonged attack, characterized by dyspnea, retrosternal oppression, anxiety, ashen pallor, and extreme weakness. There was no sweating, chill, or fever. At about the same time he noticed that his left arm was useless, and the next day it was painful. Later there was transient edema of this hand and both ankles. Seven days before admission he developed a cough which was productive of thick, white sputum.

Physical Examination.—The temperature was 97.6° F.; the heart rate, 118; the pulse rate, 80; and the respiratory rate, 32. The arterial blood pressure was 120/100. The patient was well-developed and dyspneic and had pallor and moderate cyanosis. Ophthalmoscopic examination revealed arteriovenous nicking and silver-wire arteries. There was left facial weakness. The neck veins were distended. The chest was emphysematous, and moist râles were heard at both bases posteriorly. The heart was enlarged moderately to the left, and there was a systolic murmur. The heartbeat was grossly irregular. The liver was palpable 4 fingerbreadths be-

TABLE

MURAL THROMBUS VENTRICLE		PERIPHERAL INFARCTS (EMBOLIC PROBABLY)	BRAIN						
L	L		WEIGHT (GM.)	CEREBRAL ARTERIOSCLEROSIS	THROMBUS OR HEMORRHAGE	INFARCT	EDEMA	ATROPHY	HORIZONTAL SECTION
0	Large	Lung, spleen, kidneys	1,200	++++ with elevated calcified plaques	0	Old, small in occipital lobe	++	+	No evidence of fresh infarct or hemorrhage
Small	Large	Right kidney	1,400	++++ especially of basilar artery	0	0	±	+	"No striking abnormalities are noted"
Small adherent	0	0	1,375	All moderately sclerotic	0	0	±	0	"Dilated cerebral veins"; no other abnormality noted
0	0	0	1,375	0	0	0	0	+	"Horizontal section at the level of the basal ganglia reveals a discrete, well-demarcated mass 5 mm. in diameter in the rt. optic radiation just posterior to the tail of the caudate nucleus. There are gelatinous, grayish-brown areas of softening about 2.3 mm. in diameter in the rt. frontal and left occipital lobes and in the rt. insular region"
0	Medium	0	1,375	+++ in all arteries of brain	0	Small, old, in tail of left caudate nucleus	±	+++	Normal
Small	Small	Right and left kidneys (leg)		++++ in all arteries	0	Small, in gray matter of right parietal lobe	++	+	Normal
0	Medium	Right kidney	1,410	Scattered yellow plaques	0	0	0	0	Normal
0		0	1,425	++++	0	0	+	0	Normal

low the costal margin, and the edge was tender. There was loss of motor power in the left wrist and fingers. Pain was produced by pressure over the left calf. All of the tendon reflexes were present. No sensory defect was elicited. Moderate edema of the ankles was present. There was some sclerosis of all palpable arteries. The pulsations in the dorsalis pedis arteries were very weak.

Laboratory Studies.—The erythrocyte count was 5,600,000; the leucocyte count, 7,700; and the hemoglobin, 14 Gm. per 100 c.c. The urine was acid, had a specific gravity of 1.024, and contained 2+ albumin and occasional hyaline casts. The blood Kahn reaction was negative, and the cerebrospinal fluid was normal. The electrocardiogram revealed auricular fibrillation, a ventricular rate of 80, inversion of T_1, and low voltage. T_2 was isoelectric; T_3 was of low voltage; and T_4 was isoelectric.

Course in Hospital.—After the first day the blood pressure fell to 100/70, and later rose. Muscle power in the hands returned. The facial weakness cleared up, and the edema and pain in the legs disappeared. Digitalis and bed rest reduced

his pulse rate to 60, and the pulse deficit disappeared. He was discharged after three weeks with a diagnosis of generalized arteriosclerosis, coronary artery disease with auricular fibrillation, and hysterical paralysis of the left arm.

The patient was followed in the cardiac clinic from Sept. 29, 1937, until Jan. 19, 1938, and progressed very well with the help of digitalis, which was given in daily doses of 1.5 to 3.0 grains. He had some dyspnea, an occasional precordial twinge, and infrequent spells of dizziness.

Second Admission.—He was admitted for the second time on Feb. 10, 1938, at 9:00 P.M. That afternoon, while he was walking down the street, he suddenly fell and was found unconscious.

Physical Examination.—The temperature was 107.6° F.; the pulse rate, 124; and the respiratory rate, 40. The arterial blood pressure was 182/138. When first seen, he was perspiring profusely and was moderately cyanotic. Extremely stertorous breathing was observed. The head and eyes were turned to the left. The pupils did not respond to light. The left eye was tightly closed. There were clonic spasms of both legs and the left arm. He had involuntary urination and defecation. The grossly irregular heartbeat was vigorous, and the impact was felt over the entire precordium. The rhythm and rate were completely altered by each convulsion. No murmur or friction rub was detected. The liver was barely palpable. There was no peripheral edema. The tendon reflexes could not be obtained on the left. They were normal on the right, and, in addition, there were positive Babinski and Chaddock reactions on the right. The abdominal and cremasteric reflexes were absent. The patient was given 0.25 grain of morphine and 12 c.c. of paraldehyde intramuscularly. When he became quiet, he was found to have a left-sided hemiplegia of the flaccid variety.

Laboratory Studies.—The erythrocyte count was 3,900,000; the leucocyte count, 17,000; and the hemoglobin, 10 Gm. per 100 c.c. Lumbar puncture revealed an initial pressure of 10 cm. of water. The cerebrospinal fluid was clear, and contained 3 leucocytes and 10 erythrocytes per cubic millimeter; the sugar was 84 mg. per 100 c.c.; the protein, 40 mg. per 100 c.c.; and the chlorides (as sodium chloride), 735 mg. per 100 c.c. The Pandy test and Wassermann reaction were negative.

Course in Hospital.—His condition remained precarious. The temperature varied from 104° to 107.6° F. The pulse rate fell from 124 to 70 and rose again to 85. The respirations gradually increased to 50 per minute. He died sixteen hours after admission, about twenty-four hours after the seizure on the street. The clinical diagnosis was thrombosis or hemorrhage of the right lenticulostriate artery, and coronary artery disease.

CASE 4.—H. S. (Unit 67496), a white man, aged 44 years, had been seen in the psychiatric, dental, and eye clinics of the hospital prior to his admission to the medical service, April 25, 1937, in a state of deep coma. From his wife it was learned that he had had "spells" since the age of 16, and in recent years they had become increasingly severe and more frequent. They occurred chiefly at night and were characterized by complete loss of consciousness, choking sounds, frothing at the mouth, muscular rigidity, and incontinence of urine. He had suffered from some exertional dyspnea and angina of effort for the preceding two years, but there had been no edema of the ankles until a week before admission, when there was slight edema at night. There had been no paroxysmal dyspnea at night. On the morning of admission he felt weak. He suddenly complained of substernal pain, and, when his wife returned a few minutes later, he had fallen to the floor unconscious.

Physical Examination.—The temperature was 99.2° F.; the pulse rate, 106; and the respiratory rate, 24. The arterial tension was only 70/50. He was unconscious,

in deep shock, sweating, and had an ashen, cyanotic pallor. An intermittent cough produced brownish sputum. There were râles at the bases of the lungs. The heart was enlarged; it measured 8 cm. to the right, and 13 cm. to the left, of the midline. The heart sounds were faint, but no murmurs or rubs were heard. The liver was palpable 3 fingerbreadths below the costal margin. Neurological examination revealed a Babinski reaction on the left, but nothing else of consequence.

Laboratory Studies.—The erythrocyte count was 4,600,000; the leucocyte count, 32,200; and the hemoglobin concentration, 16 Gm. per 100 c.c. The blood Kahn reaction was negative. Blood chemical studies revealed a urea nitrogen of 30 mg. and a carbon dioxide combining power of 39 volumes per 100 c.c. Urinalysis showed 1+ sugar, with occasional leucocytes and casts in the sediment. The electrocardiogram was typical of posterior infarction.

Course in Hospital.—The temperature reached 101.5° F. on the second hospital day. The pulse rate gradually fell, and a systolic murmur appeared. A diagnosis of coronary occlusion was made. He was instructed to take digitalis and remain at rest in bed for six weeks.

Second Admission.—He was readmitted, this time on the neurological service, on June 15, 1937, in a state of deep coma. His wife stated that he had systematically disobeyed instructions, i.e., had walked about, climbed stairs, and worked. The day before admission he was apparently as well as ever. The next day, at 5:30 A.M., he had one of his usual "spells," with grunting breathing, unconsciousness, and incontinence of urine. This lasted for twenty minutes. He had another attack at 6:30 A.M., and another at 7:30 A.M., after which he was admitted. These were identical with his regular epileptic seizures, as far as his wife could tell, except that there was profuse sweating between attacks.

Physical Examination.—The temperature was 101.4° F.; the pulse rate, 120; and the respiratory rate, 42. The arterial blood pressure was 100/80. The patient was in deep coma, cyanotic, and sweating, with rapid, shallow breathing. There were slight abrasions on the head about the right occipital region. A few fine râles were heard at the base of the right lung. The heart was enlarged, and a rough systolic murmur was heard. The heart sounds were of very poor quality. The liver was barely palpable. The neurological examination showed nothing remarkable.

Course in Hospital.—He rapidly developed bilateral ankle clonus and positive Babinski and Chaddock signs. He began to turn his face regularly to the left. He had generalized rigidity, especially on the left. Signs of pneumonia of the right lower lobe developed, and a Type XIII pneumococcus was recovered from the sputum. His temperature and pulse rate rose rapidly. It was believed by members of the house staff and visiting staff that the clinical manifestations could best be explained as postepileptic exhaustion complicated by bronchopneumonia. The patient died on the third hospital day.

CASE 5.—L. S. (Unit 89077), an 87-year-old colored man, was admitted to the neurological service March 2, 1938, in a comatose condition. The history, obtained from a friend, indicated that he had been well until a week before admission, when he developed a "toothache" and a headache in the left temporal region. He was aroused with difficulty on the morning of admission and said he felt queer. He was still confused in the afternoon, and shortly before he was brought to the hospital he became aphasic. Twitching of the right side of the face, right arm, and right leg was observed. No cardiac symptoms had been noted.

Physical Examination.—The temperature was 100.8° F.; the heart rate, 110; the pulse rate, 66; and the respiratory rate, 30. The blood pressure was 160/100. The patient was comatose, and his entire right side was involved in rapidly repeated

involuntary twitching movements. The pupils were irregular, the right more so than the left; both reacted sluggishly to light. The cyanotic tongue had been bitten recently, exhibited twitching, and was deviated to the left. The neck veins were distended. Râles were heard at the bases of the lungs. The heart was enlarged. The heartbeat was grossly irregular, and the sounds were of fair quality. Marked sclerosis of the superficial arteries was noted. There was no edema. Neurological examination revealed a complete right hemiplegia when he was not twitching. The pectoral, biceps, and triceps reflexes were equal. The knee and ankle jerks were present on the left, but absent on the right. There was a questionable Babinski and Rossolimo reflex on the right.

Laboratory Studies.—The erythrocyte count was 4,200,000; the leucocyte count, 9,500; and the hemoglobin, 14 Gm. per 100 c.c. The urine was alkaline, of a specific gravity of 1.025. It contained 3+ albumin and a few leucocytes and granular casts. The blood Kahn reaction was negative. Blood chemical studies revealed a urea nitrogen of 32 mg. and a carbon dioxide combining power of 44 volumes per 100 c.c. The cerebrospinal fluid was clear, with an initial pressure of 12 cm. of water; there were 10 leucocytes per cubic millimeter. The protein was 48 mg. per 100 c.c.; the sugar, 65 mg. per 100 c.c.; and the chlorides, 682 mg. per 100 c.c. The electrocardiogram showed left axis deviation. The QRS complexes were slurred in Leads II and III. T_4 was inverted; $S\text{-}T_1$, elevated; and $S\text{-}T_3$, depressed. There were extrasystoles from three foci in the ventricle.

Course in Hospital.—The pulmonary edema increased, and the patient died on the third hospital day, in spite of digitalization and other treatment. The blood pressure did not fall below 140/100 until just before death. The clinical diagnoses were cerebral hemorrhage into the left internal capsule, with right hemiplegia, and arteriosclerosis of the coronary arteries. One observer suggested the possibility of a subdural hematoma.

CASE 6.—R. T. (Unit 106527), a 61-year-old colored man, was admitted to the surgical service Oct. 31, 1938, with a complaint of pain in the left leg and foot. The past history was not accurate, but he had had exertional dyspnea for several years, with intermittent claudication and occasional edema of the ankles which disappeared at night. For five years he had had frequent attacks of precordial pain which were precipitated by exertion or emotion. There had been attacks of dizziness and "spots before the eyes." Three weeks before admission he had had a right-sided hemiplegia, with aphasia, which lasted only a few hours. Two weeks before admission he had a syncopal attack, after which his mind had been cloudy. One week before admission he had "blind staggers," with vague epigastric pain, for which he had consulted his family physician. The day before admission, while walking, he had a sudden, severe pain in his foot and the inner portion of his left leg.

Physical Examination.—The temperature was 97.2° F.; the pulse rate, 92; and the arterial blood pressure, 170/110. He was moderately obese and was apprehensive at times. He was comfortable lying flat in bed, but his neck veins were engorged. The heart was enlarged to the left. The sounds were of poor quality, and there were numerous extrasystoles. No murmurs were heard. Moist râles were detected at the bases of the lungs. The left leg was swollen and cold, and no pulse was felt below the femoral artery. The reflexes were normal.

Admission Laboratory Studies.—The erythrocyte count was 4,300,000, and the leucocyte count, 15,000. The urine was acid, with a specific gravity of 1.017; it contained 4+ albumin, leucocytes, and granular casts. Lumbar puncture revealed a normal cerebrospinal fluid under a pressure of 22.5 cm. of water. The blood urea nitrogen was 29 mg. per 100 c.c., but fell to 14 on the third day. On the seventh hospital day the carbon dixoide combining power was 54 volumes per 100 c.c.

Course in Hospital.—The leg improved somewhat with passive vascular exercise. On the third night after admission the patient became irrational, got out of bed, and wandered around. He was completely disoriented, and there was a sudden rise in temperature to 102° F.; the pulse rate reached 110. He expressed a fear of death. He was slowly digitalized, but gradually grew worse. Eight days after admission a medical consultant saw him and noted profuse sweating, coma, deep, stertorous breathing, and pulmonary edema. The tongue deviated to the right. The right arm was flaccid. The abdominal and cremasteric reflexes and the knee jerks were absent. There were no reactions to plantar stimulation and little reaction to painful stimuli. It was suggested that the patient had a cerebral hemorrhage. Another lumbar puncture showed that the spinal fluid was still normal. The electrocardiogram revealed a rate of 80, with sinus rhythm and left axis deviation. The QRS complexes were slurred and of low voltage in all leads. The P-R interval was 0.22 to 0.24 second. T_1 and T_4 were inverted. T_2 was isoelectric, and T_3 showed low voltage. He developed Cheyne-Stokes respiration. The temperature rose to 106.8° F., and the patient died on the ninth hospital day. The clinical diagnosis was probable cerebral accident. One observer suggested the possibility of coronary occlusion.

Case 7.—G. C. (Unit 104989), a 53-year-old colored man, was admitted to the medical service Oct. 19, 1938, with the complaint of being "choked up and stopped up in the head." The family history revealed that his father had died of "acute indigestion" and his mother of heart trouble, and, of six dead siblings, three died of heart trouble of an unspecified variety. At the age of 18 years he had had typhoid fever which was followed by enlargement of the right leg. This had been treated seventeen years later by excision of varicose veins. He had had a chancre sixteen years before. At times he had experienced sharp epigastric pains when he had "gas on the stomach." He had had attacks of dizziness and headache for approximately one year. His present illness began four months before admission with a severe attack of asthma, which lasted thirty-six hours and left him with a chronic cough and occasional attacks of paroxysmal dyspnea. He stopped work until a month before admission, when he took a job as hod carrier and worked for a week. One day while at work he was seized with a sudden, severe attack of dyspnea and weakness. There was no pain then or later. He had increasing dyspnea and orthopnea, with edema of his good and bad leg. He was admitted because of the increasing dyspnea.

Physical Examination.—On admission the temperature was 99.6° F.; the pulse rate, 116; and the respiratory rate, 36. The arterial blood pressure was 170/134. He was a severely dyspneic colored man with an anxious expression, and was propped up in bed. At times he coughed up frothy sputum. The neck veins were engorged. Moist râles were heard throughout the chest. The heart was markedly enlarged, with dullness 14 cm. to the left of the midline in the sixth intercostal space and 4 cm. to the right in the fourth intercostal space. There was a suggestion of gallop rhythm at the apex, and the aortic second sound was very loud. The liver extended 4 fingerbreadths below the costal margin, and was tender. The right leg was edematous and was the seat of extreme fibrosis; there was an ulcer on the shin which measured 3 by 6 cm. The left leg was swollen also, but only to half the size of the right. Neurological examination was negative.

Laboratory Studies.—The erythrocyte count was 3,500,000; the leucocyte count, 6,800; and the hemoglobin, 10.7 Gm. per 100 c.c. The urine was acid; its specific gravity was 1.038; it contained 2+ albumin and a few leucocytes and erythrocytes; many hyaline and granular casts were found in the centrifuged specimen. The blood Kahn reaction was negative. The blood urea nitrogen was 23 mg. per 100 c.c. The clear cerebrospinal fluid had an initial pressure of 23 cm. of water; there

were 2 leucocytes per cubic millimeter, the protein was 16 mg. per 100 c.c., and both the Pandy test and Wassermann reactions were negative.

Course in Hospital.—He was treated with morphine and aminophylline and was digitalized rapidly. His pulse rate fell to 100; his respirations, to 10. The temperature remained the same. Early in the morning of the second hospital day he suddenly became unconscious, had Cheyne-Stokes respiration, and lost all of his reflexes except a slow corneal response. The blood pressure was 74/50. There were no signs of pyramidal tract disease. He died three hours after the onset of the unconsciousness. The clinical diagnosis was cerebral hemorrhage, in addition to the admission diagnosis of hypertension and arteriosclerotic coronary artery disease, with severe cardiac failure, and elephantiasis and ulceration of the right leg.

CASE 8.—R. F. (Unit 49873), a 45-year-old colored man, was admitted to the surgical service Dec. 30, 1935, with frostbite of both hands which he incurred when shoveling snow on Christmas Eve. There was nothing in the history to suggest cardiac disability of any kind.

Examination.—The temperature was 100.6° F.; the pulse rate, 106; and the arterial blood pressure, 130/90. The heart was normal in all respects. The liver was barely palpable, but not tender. No edema was present. First degree frostbite of both hands was observed. A single urine specimen was negative. The blood Kahn reaction was strongly positive (3+).

Course in Hospital.—The patient was treated with passive vascular exercise for twenty minutes a day, twelve times during the first three weeks in the hospital. There was some sloughing of the fingers, which were débrided from time to time. He was progressing well when he suddenly became severely nauseated early in the morning of the thirty-sixth hospital day, and complained that he had slept poorly. He was given peppermint water and, at 9:00 A.M., vomited several times. At noon he felt better and was walking about the ward, when he suddenly fell across a bed and began to have stertorous respiration. Within about one minute his pulse and heartbeat were imperceptible, and his respirations grew irregular. He died seven minutes after the syncopal attack began. His jaws were clamped tightly together. No other neurological abnormalities were found. Intracardiac injections of adrenalin and caffeine did not revive him. It was believed that he had a cerebral hemorrhage, thrombosis, or coronary occlusion.

COMMENT

These cases revealed a variety of cerebral symptoms in association with acute cardiac infarction. Hemiplegia, coma, syncope and shock, epileptic convulsions, vomiting, and mental disturbances, with confusion and delirium, were some of the manifestations. The physiologic factors concerned with the various types of symptoms are obscure, but it is reasonable to suppose that cerebral arteriosclerosis, together with reduced blood flow, was the major localizing factor. Each case must be individualized in order to understand the mechanism concerned.

Certain general observations are justified. The diagnosis of infarction of the heart is very difficult from physical examination alone. When the sensorium is clouded, and no history is available, it may be overlooked. This is particularly true when neurological signs point to a localized lesion in the brain. These cases indicate that marked neurological disturbances may occur in infarction of the heart, without any acute or rapidly progressing vascular lesion in the brain. The reason

probably is that relative ischemia of the brain occurs because the heart is hypodynamic. In an area in which the caliber of the arteries is fixed, blood flow is influenced by arterial pressure and the rate of the circulation. When the pressure falls, the flow is reduced. From the literature which has been cited, it is clear that a fall in arterial tension may produce focal neurological signs in the presence of arteriosclerosis of the cerebral vessels. It is assumed that the location of resulting neurological disturbances is determined by the distribution of the cerebral vascular constrictions.

It is possible that reflexes from the heart to the brain may produce similar cerebral manifestations. This is true of carotid sinus syncope.[14] Nothing is known of the exact mechanism in such cases, but one suspects that changes in the caliber of the cerebral vessels are concerned.

In the instances in which pulmonary congestion is marked, anoxemia is added to the damage produced by the focal ischemia of the brain. Ischemia, when the blood is well oxygenated, is naturally less deleterious than when blood is poorly oxygenated.

It may be of importance that all of our patients were men. More than the expected proportion were colored. Except in Case 4, all showed severe arteriosclerosis, particularly in the medium-sized arteries.

We wish to stress, finally, the tendency of each patient who had more than one attack to exhibit similar manifestations in each. This emphasizes an important, though often neglected, point. Disease of whatever kind is superimposed upon the substratum of the patient. His physical makeup, if it deviates far from the norm, will reflect disease in an aberrant form.

SUMMARY AND CONCLUSIONS

Clinical and morphologic data are presented in eight cases in which there were symptoms of acute cerebral disease associated with infarction of the heart. No clinical diagnosis of heart disease was made because the bizarre central nervous system manifestations obscured the picture.

The most likely cause of this unusual syndrome is that a fall in arterial blood pressure reduces cerebral circulation. When the cerebral vessels are narrowed and rigid from sclerosis, the resulting ischemia gives rise to focal signs. Congestive failure, with its attendant anoxemia, may increase the local anoxia of the brain.

In an epileptic patient, cardiac infarction was associated with a series of convulsions which were similar to the ordinary seizures.

These cases show that there are aberrant forms of a well-recognized syndrome. The abnormal physical substratum of the patient distorts the clinical picture by producing complications which camouflage the main disorder.

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QUANTITATIVE MEASUREMENT OF REACTIVE HYPEREMIA IN HUMAN SKIN

Individual and Seasonal Variations

Joseph R. Di Palma, M.D., Samuel R. M. Reynolds,* Ph.D., and Frances I. Foster, B.S., Brooklyn, N. Y.

THE immediate object of this study was to establish a simple, reliable technique for the estimation of functional changes in the condition of the smallest blood vessels in human skin. This paper is concerned with the second of two such methods. The first of these, which was reported elsewhere,[1] depends largely upon the contractile sensitivity of the smallest blood vessels of the skin to graded mechanical stimulation; the present method measures the capacity of these vessels to respond by reactive hyperemia to a given period of local ischemia. The fact that the amplitude and duration of the response are dependent largely upon the duration of circulatory stasis was established by Lewis[2] and confirmed by others.[3-5] It appeared, therefore, that a procedure could be devised whereby local ischemia might be maintained for a time just sufficient to elicit a given degree of reactive hyperemia. This would then serve as a measure of the reactive capability of the smallest blood vessels in the skin. The present paper, in recording such a method, notes certain seasonal, individual, and physiologic factors which affect this property of the cutaneous blood vessels and tissues.

The uses of such a measure of skin function are several. Its chief value should be to provide a means of estimating how disease, physiologic processes, and therapeutic agents affect the capacity of the skin to yield substances which give rise to reactive hyperemia.

METHODS AND PROCEDURES

This method for measurement of reactive hyperemia in the skin depends upon a suitable instrument and an adequate procedure for its application.

An instrument was devised to enable one to apply weights with deftness and accuracy to the forearm of a subject for varying lengths of time. As can be seen in Fig. 1, this aim was attained by mounting three pans on levers, made of Brown and Sharp 9 gauge wire, which limit their motion to an arc in a vertical plane perpendicular to the axis of the forearm. The lifting and lowering lever is made

From the Department of Physiology, Long Island College of Medicine, Brooklyn.

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*Research Associate, Carnegie Institution of Washington, Baltimore, Md., Sept. 1, 1941.

of the same wire and is arranged with enough mechanical advantage so that the pans may be lowered slowly and gently upon the arm.

The construction details are simple. The top plate (Fig. 1) is of heavy-gauge, galvanized iron, 11 by 15 inches in size, with a rectangular, 1.75 by 6 inch cutout at one end. The lower portion is made of 0.75 inch wood stock and is about 5 inches deep. It was found advisable to cover the under side of the region bordering the cutout in the plate with velvet or felt in order to forestall any possible blood vessel reaction caused by contact of cold metal with the skin. The weight holders, or pans, are the lower portions of 1 oz. salve tins. Although any substance might conceivably be used for the actual application portion of the pans, we found in practice that the following arrangement was the most efficient. A strip of rubber, 0.5 by 0.5 by 10.0 cm. in size, is shaped into a circle and cemented in the center of a disc of metal 4.5 cm. in diameter. This disc, in turn, is cemented to a layer of sponge rubber, and, finally, the whole is applied to the bottom of the pans. The discs are curved slightly to fit the contour of the arm. It is also desirable to smooth with fine emery paper the sharp edges from the rubber applicator rings in order to prevent cutting into the skin. This would falsify the end point of the reaction, as noted below.

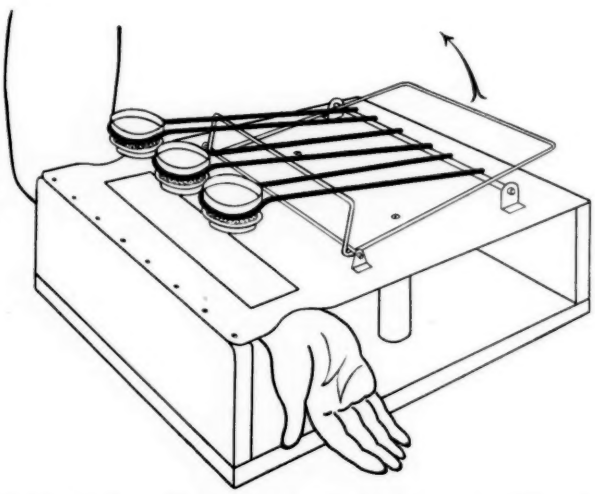

Fig. 1.—Diagram of instrument with which three areas of reactive hyperemia may be made simultaneously upon the inner aspect of the arm. By ascertaining the minimal length of time necessary to just induce rings of uniform color, size, and sharpness, one may obtain a measure of reactive hyperemia. (See Fig. 2 and text for discussion.)

Thus it is seen that the whole arrangement is designed to provide a maximum of application despite variations in arm contour and unavoidable position differences of different arms. The use of equal weights (500 Gm.) in the three pans and their application over three areas of equal size and shape offer ample opportunity for comparison of the several responses. This was found to be desirable. The actual application surface of the rubber rings amounts to approximately 5 sq. cm. (0.5 by 10 cm.). Thus the load is 100 Gm. per square centimeter.

Procedure.—Observations are best made in a quiet room, free from drafts, and at a room temperature of about 70° to 75° F. The subject is seated in a comfortable position, with the arm inserted in the supine position. It is supported snugly, but not tightly, in place by a rubber wedge. The subject should rest for several minutes.

The field is illuminated by two blue (photographic), 100-watt mazda lamps, with reflectors, placed at a distance of about two feet from the arm. These are focused to one side of the cutout on the instrument.

As the weights are applied quickly to the skin, a stop watch is started. The weights are left in place for a suitable length of time (see below), then lifted off swiftly, and the ischemic areas watched closely for the color pattern, its course of development, and duration. After the areas are well cleared, the position of the arm is shifted slightly, and the effect of another period of ischemia is ascertained until the threshold level is obtained. The threshold is ascertained in the following manner.

The Threshold Response.—Judgment as to what constitutes the end point in any one observation depends upon the color quality, the texture, the discreteness of the edges, and the width of the rings which result from stimulation for graded lengths of time, as described above. When the period of ischemia (''stimulation-time'') is relatively short, release is followed by blanching of the area of application. In two to three seconds the blanched area begins to fill in with a purplish hue which builds to a maximum intensity in twelve to eighteen seconds. At this time, careful observation reveals that the texture is mottled, the edges uneven, and the width somewhat less than 0.5 cm. The rings may be incomplete. This is a subthreshold response (Fig. 2*C*). When the stimulation time is increased, a point is reached at which the color becomes bright red, the rings are of even texture and have discrete edges, and the width approximates 0.5 cm., i.e., the exact size of the application area. This constitutes a threshold response (Fig. 2*D*). Relatively high stimulation times (over the threshold) cause very bright red rings which are larger than 0.5 cm. in width and are surrounded by an arteriolar flare (Fig. 2*B*). Various degrees of responses may, of course, be obtained, depending on the stimulation time, but the observer, by trial and error and by adopting a standard routine, soon learns to pick out the threshold with an accuracy of two to five seconds. At the threshold, the time that is taken for the rings to fade to the hue of the surrounding skin is noted. This constitutes the ''clearing time'' and normally equals or exceeds the stimulation time.

When the weight loading is less than 15 Gm. per square centimeter, relatively long stimulation times (five to ten minutes) produce only cyanotic, narrow rings in every instance (Fig. 2*A*). By experiment it was found that a loading of at least 20 Gm. per square centimeter had to be used before the red flush of reactive hyperemia could be obtained with short stimulation times. As the loading is increased up to 100 Gm. per square centimeter, not only is the resulting reactive hyperemia more intense, but the threshold is shortened.

It is generally agreed that capillary pressure extends, on an average, from 12 mm. of mercury in the venous end to 32 mm. of mercury in the arterial end of the capillary loop (in the finger). Simple calculation shows that this corresponds to a weight loading of roughly 16 Gm. per square centimeter for the former, and 44 Gm. per square centimeter for the latter, and that this is just sufficient to cause ischemia of the vessels, not counting the resistance of the tissues themselves. Since weight loadings of 15 Gm. or less do not cause reactive hyperemia, it must be inferred that complete occlusion of at least the venous end of the capillary loop is requisite for the threshold response. Furthermore, the increasing intensity of the reactive hyperemia and the decrease in the threshold with weight loadings which exceed purely occlusive pressures suggest that there is an added factor of tissue injury. This agrees with the observations of Lewis[2] and is important in the study of the results and discussion which follow.

RESULTS

Individual Responses.—In July, 1940, at the outset of this study, the minimal length of time necessary to elicit the liminal response (Fig. 2*D*) ranged from four seconds in one subject to eleven seconds in another. The subliminal response (Fig. 2*C*) was read to within two seconds in each case. Repeated observations on five subjects at this time

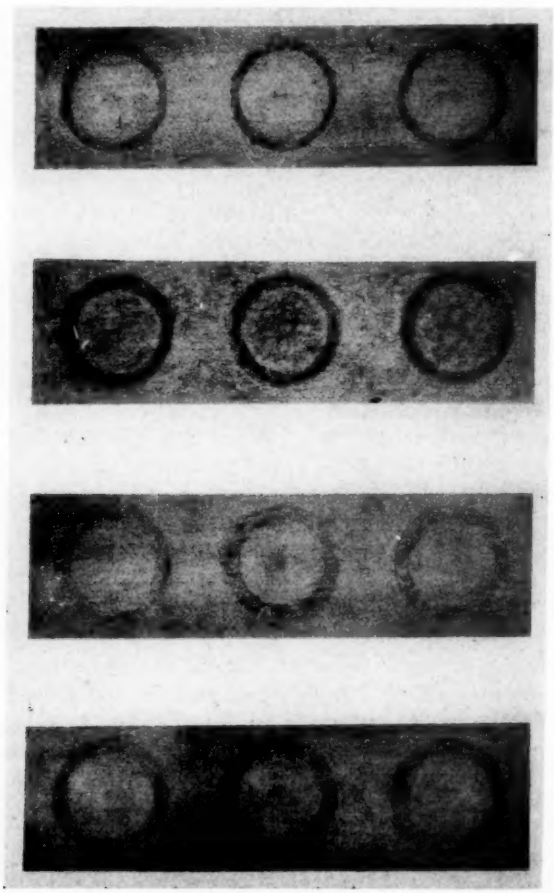

Fig. 2.—Drawings of the types of response which may be elicited with the device shown in Fig. 1. *A*, Cyanotic rings; *B*, maximal response with reflex flare; *C*, just subliminal response (diffuse edges, uneven width, and mottled appearance); *D*, threshold response, induced by application of the weights for a time just long enough to give rise to rings of uniform color and size, with discrete edges.

gave values which fell within this range. On any given day, the threshold response remained constant at this season of the year. It was unaffected by ordinary degrees of activity and not modified in any regular way by meals. This was tested by examining threshold levels on subjects with a normal caloric intake and those with very low or no caloric intake. The positions of these subjects were then

reversed and the thresholds again examined. No significant change was noted. With regard to exercise, no appreciable difference was observed in the threshold level of reactive hyperemia in the skin immediately before exercise and immediately afterward (stepping on and off a stool 100 times within a few minutes). Similarly, after the patient had rested, recumbent, for an hour, the threshold was found to be unchanged. Accordingly, moderate changes in body metabolism exert no immediate influence upon the capacity of the cutaneous vessels to give the reactive hyperemia response.

Observations were also made on the possible influence of psychic factors.[6] Subjects who presented evidence of emotional instability, as noted from time to time by the student health office, were studied, and in other subjects the hyperemia threshold response was examined before and after acute psychic stimulation. Our conclusions were that, although prolonged psychic upsets might alter the threshold even during the course of its determination, acute psychic trauma did not have a discernible effect. Accordingly, all subjects who were suspected of emotional instability were eliminated from the series reported in this paper.*

Seasonal Variations.—As the summer ended and fall advanced, a gradual and progressive change was found in both the stimulation time and the clearing time of the response. By September, the threshold was thirty to thirty-four seconds in duration, and the clearing time averaged about forty seconds. By December, these values were more than doubled (Fig. 3).

The change in the time course of the reactive hyperemia response was not the result of conditioning of either the subjects or their skin to the process of repeated stimulation employed in this study. This is attested by the fact that, as the threshold values increased progressively with the season in the initial group, data obtained from new subjects who were recruited throughout the fall and winter showed similarly high threshold and clearing time values. Specific instances of this in a few cases are summarized in Table I.

Throughout the more than eleven months spanned by this study, over 500 observations were made on more than 100 subjects. This group was comprised of medical students (male and female), laboratory workers, and members of the teaching staff. Still others, whose responses were comparable in every way to those of the main group of subjects, were two male castrates and two eunuchoid subjects. The composite curve of the average weekly thresholds and clearing times is shown in Fig. 3, along with data on external weather conditions compiled from the official weather reports of the New York area, and on the mean temperature and relative humidity which prevail in the laboratory throughout the year.

*For the sake of brevity, detailed data on this phase of the problem have been omitted.

The seasonal character of the data is unmistakable. The periods of change seem to coincide inversely with two conditions, namely, external temperature and indoor humidity. Despite the fact that most of our subjects were exposed to outside weather for only two hours a day, or less, throughout most of the year, it seems probable that the seasonal variation in reactive hyperemia is affected by external temperature

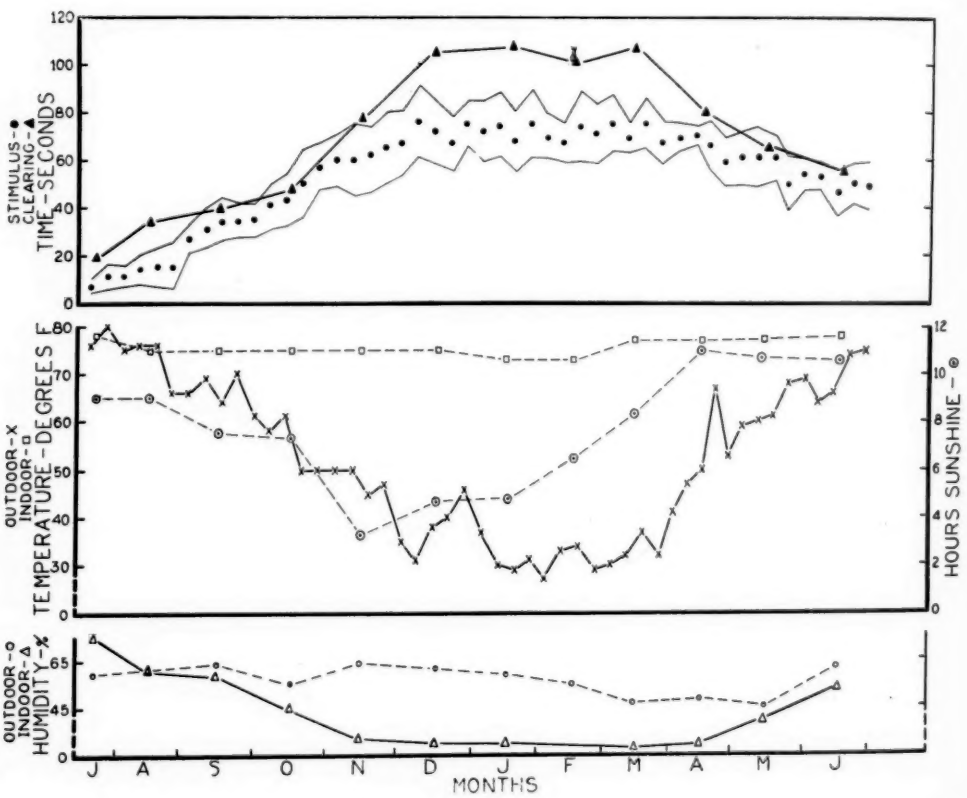

Fig. 3.—Curve of the average weekly threshold response of reactive hyperemia (dots), and clearing times for the response (triangles), from July, 1940, through June, 1941. Range of standard deviation, light lines. Data on external weather conditions were compiled from official weather reports and indoor laboratory conditions from day to day. More than 500 observations were made on over 100 subjects. Weekly averages contain no more than one reading from any single subject.

rather than indoor humidity, for heat loss and body adjustments to temperature are affected by dry-bulb, rather than wet-bulb, readings.[7, 8] The clearing times show a seasonal variation, along with the stimulus times. The average weekly curves show that the two phenomena do not parallel each other, however. The stimulus time lengthened appreciably before the clearing time, but, in the spring, the latter underwent a change long before the former. The clearing time, as will be seen

in Fig. 3, correlates more closely with the change in external temperature than does the stimulus time. Since, as will be shown below, the clearing time is affected to a large degree by the rate of blood flow through the skin, and this, in turn, is influenced to a large degree by the temperature of the environment,[9,10] the foregoing correlation is consonant with known facts.

TABLE I

DATA SHOWING THE SIMILARITY IN THRESHOLD VALUES OF REACTIVE HYPEREMIA BETWEEN FIRST OBSERVATIONS ON NEW SUBJECTS AND ON TWO WHO WERE USED FROM OUTSET

DATE	SUBJECT A		SUBJECT B		NEW SUBJECTS, FIRST READING		
	THRESHOLD (SEC.)	CLEARING TIME (SEC.)	THRESHOLD (SEC.)	CLEARING TIME (SEC.)	SUBJECT	THRESHOLD (SEC.)	CLEARING TIME (SEC.)
July 25	3-6	17			H	8-10	27
30	6-8	19	6-8	27			
Aug. 1			8-10	24	C	8	28
8			12-14	32	F	10-12	27
Sept. 3	25-28	47	28-30	39			
9	30-33	39			G	22-25	35
19	33-35	38					
21			24-26	38			
24	20-23	39			E	30-33	33
26			43-45	55	D	28-30	36
Oct. 3	30	35					
8					I	45-48	39
14	43-45	46			J	43-45	51
23	38-40	41			K	45-50	61

The Response During Circulatory Stasis.—The effect of complete circulatory stasis upon the threshold and clearing times was studied. This was done in order to ascertain to what extent the response depends upon a continuous flow of blood. The results of such experiments are summarized in Fig. 4.

Occlusion of the circulation for five to fifteen minutes was found repeatedly, and at different times of the year, to have no effect on the threshold time. As long as the circulation was occluded, however, the colored rings failed to clear. Under the conditions of these experiments, therefore, the threshold is not modified by cessation of blood flow, with all that that entails, but the disappearance of reactive hyperemia requires the circulation of blood. This agrees with the qualitative observations of Lewis,[2] but only in part with those of Goldschmidt,[11] who observed that reactive hyperemia continues for a long time when the arm is in normal atmospheric air but disappears rapidly (in the skin) when the arm is surrounded by pure oxygen.

The Response After Release From Stasis, i.e., During Reactive Hyperemia.—The thresholds and clearing times were studied during reactive hyperemia, after circulatory stasis. In contrast to the conditions described above (in which the response was studied during stasis), the

threshold is appreciably increased when the test is made during the period of increased blood flow (Fig. 4*B*). In view of the fact that cessation of blood flow has no effect upon the threshold when it is measured during stasis, this increase in the threshold with increased blood flow could be explained by more rapid dissipation of a vasodilating substance. By the same token, the elevated threshold times would then result from the necessity for greater production of a dilating substance, in order to offset an increased rate of removal.

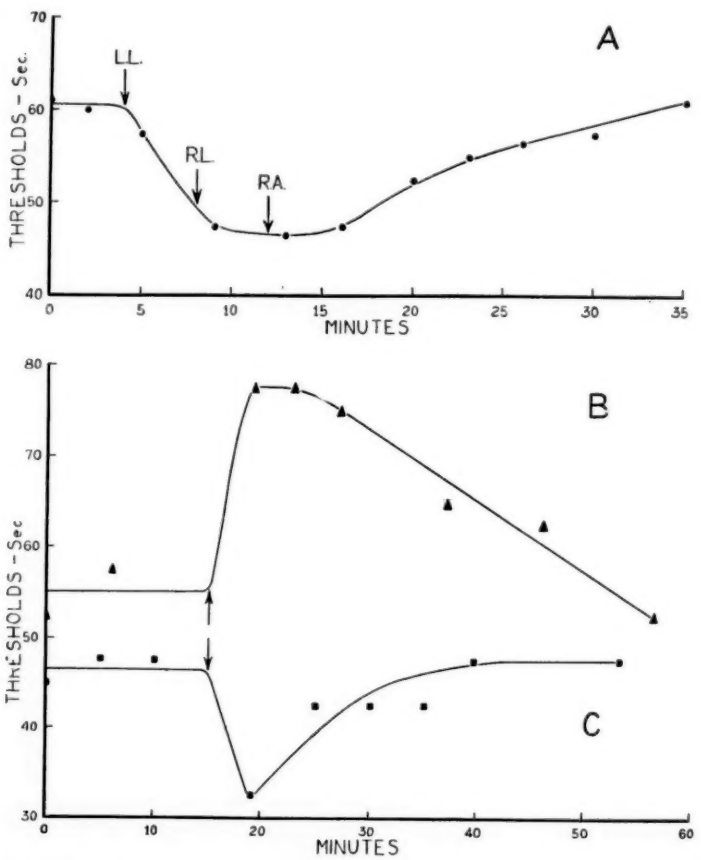

Fig. 4.—Effects of circulatory stasis on threshold responses. *Top*, the effect in the left arm after release of stasis after five minutes in the left leg (*L.L.*), ten minutes in the right leg (*R.L.*), and fifteen minutes in the right arm (*R.A.*). This shows the presence throughout the body of the products of stasis, without effect on heart rate or blood pressure. *Middle*, the effect on threshold during period of reactive hyperemia after release from stasis in the same arm (i.e., with augmented blood flow). *Bottom*, the effect on threshold after release from stasis (same arm), but with the circulation momentarily occluded during the tests. (See text for discussion.)

The foregoing inference is supported by another type of experiment. The circulation was temporarily occluded during reactive hyperemia, at the time the test reading was being made. Significantly, the threshold was found to be transiently lower than the control, or normal,

threshold (Fig. 4*C*). The higher threshold in the presence of an unrestricted, augmented flow of blood through the skin (Fig. 4*B*) is the result, therefore, of the requirement for more dilating substance to make up for its rapid removal. The lowering of the threshold during the initial phase of the period of reactive hyperemia in this experiment needs explanation, inasmuch as stasis alone does not alter the threshold. This explanation was found in the following experiments.

In a recumbent subject, the circulation was occluded at both knees and above the right elbow. The stimulus and clearing times were measured at four- or five-minute intervals in the left forearm. At the end of five minutes' occlusion, the circulation was released in the left leg; after ten minutes, it was released in the right leg, and after fifteen minutes, the circulation of the right arm was re-established. Although there was no change in heart rate, or systolic and diastolic blood pressures,[5] a marked *decrease* in the threshold for reactive hyperemia was encountered in the left arm. After release from circulatory stasis, therefore, a substance is presumably washed away during reactive hyperemia which affects the threshold for reactive hyperemia in a remote part of the body (Fig. 4*A*). It is therefore clear that the lower threshold in an arm with reactive hyperemia (and with the circulation momentarily occluded, as in Fig. 4*C*) is attributable to the presence in the affected tissues of some dilating substance or substances. Hence a less than normal additional stimulus suffices to evoke the reactive hyperemia response. The evidence that there is a washing away of the vasodilating substance during hyperemia is therefore threefold: (1) With stasis alone the stimulus time is unaffected, but the rings do not clear; (2) with increased blood flow, greater stimulation is required to evoke the response; and (3) the effect of this dilating substance has been shown upon washing away on remote tissues which are not directly involved in the production of the substance.

The reason why the threshold during simple circulatory stasis without previous hyperemia is unchanged must remain for the present without an explanation based on facts. It appears paradoxical that, during occlusion of the circulation, a substance is produced which will alter the threshold *after* the circulation is re-established, but does not affect the threshold unless this condition is fulfilled. The view advanced by Lewis[2] is consonant with our observations. This author postulates that the dilating substance is produced intracellularly and that it cannot be brought into contact with the blood vessels unless the flow of blood is re-established. Likewise in agreement with Lewis is our observation that tissue trauma (in the present case, application of the weights causing ischemia) will effect release of some of the dilating material and thus permit the local appearance of reactive hyperemia in an arm which is the seat of circulatory stasis. In summary, these considerations show that the clearing time of the response is affected by certain alterations

in blood flow through the skin and that the stimulus time is thus influenced *indirectly* by the rate of removal of the dilating substances produced during the period of ischemia. This conclusion seems at variance with the seasonal curve, however, for blood flow in the skin increases in warm weather[9, 10] and so might contribute to the shorter clearing time which is present in the summer months, but it fails to account for the similarly shortened stimulus time in the summer. This, it appears, must be accounted for by seasonal fluctuations in the capacity of the tissues to produce dilating substances, or by altered sensitivity of the blood vessels, or both.

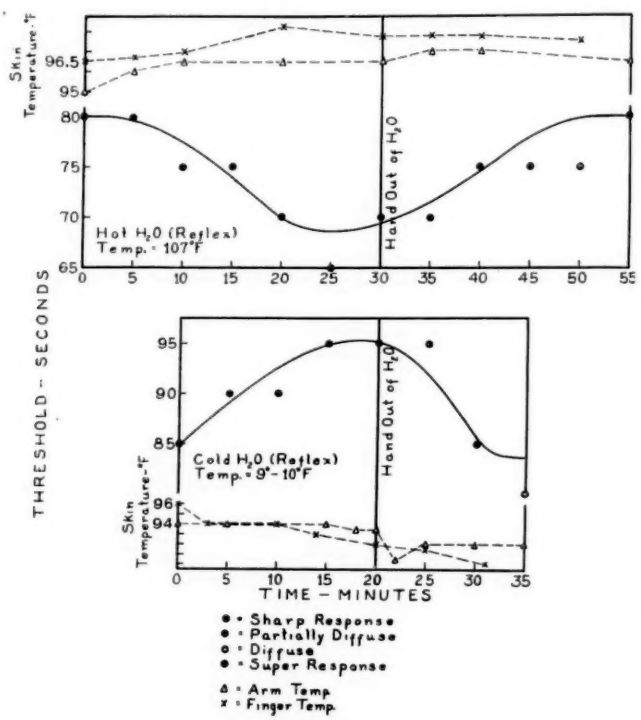

Fig. 5.—Effects on threshold reflex response to warmth (*top*) and cold (*bottom*). (See text.) (9° to 10° F. should read 9° to 10° C.)

Reflex Effects.—The influence of reflex response to temperature change was investigated. In these experiments, the threshold was ascertained in the usual way, at five-minute intervals, on the left arm. After the normal threshold level was established, the right hand and the arm (up to the mid-point) were immersed in water. In order to study the effect of cold the water was kept at a temperature of 9° to 12° C., and, for the effect of warmth, the temperature was 41° to 42° C. The skin temperature of the left arm and a finger of the left hand (nail bed area) was measured by means of a continuous recorder. In this way, threshold levels could be related to the reflex effects of temperature on

the circulation. Although it is now generally believed that the skin of the forearm does not participate to any significant degree in reflex readjustments to temperature changes,[5] it was considered desirable to record such data. The results of two experiments of this type are summarized in Fig. 5. The threshold is clearly affected by reflex responses to temperature; with cold, the threshold was raised, and, with warmth, it was lowered. The duration of the effect outlasted the period of immersion, but there was a return to normal before the skin temperatures became normal. Since slight changes in blood flow have little effect on the stimulus time (cf. above, effect of meals and exercise), one may conclude that reflex temperature adjustments have a considerable influence upon the ease with which reactive hyperemia may be induced in the skin.

These results may shed light on some aspects of the seasonal curve. Thus, the higher thresholds are found during the colder periods of the year, and the lowest thresholds, at the hottest part of the year. It appears probable that the generalized heating of the surface of the body in the summer may reflexly cause a lowering of the stimulus time threshold despite the fact that one would expect an opposite effect caused by the augmented blood flow which is known to exist under such conditions. The same reasoning holds for the winter season.

Actual analysis of the seasonal chart (Fig. 3), it should be re-emphasized, shows that the effects of warmth on the threshold curves are not immediate and do not follow the day-to-day weather fluctuations. Nevertheless, two downward steps on the threshold curves were obtained in the latter part of April and in May, and these occurred on days that were unseasonably warm. The return to cooler and more normal weather, however, marked merely a break in the downward trend of the threshold curve and not a return to the longer thresholds of a week or two earlier. These considerations pointed to the need for experimental study of a direct change in skin temperature on the threshold.

Direct Heat.—With a normal skin temperature of 90.2° F., the threshold for reactive hyperemia was thirty seconds, and the clearing time, forty-one seconds. After the skin was warmed by the application of external heat, and while the skin temperature was held at a level of 97.7°–98.0° F., the stimulus time was twenty-one to twenty-two seconds, and the clearing time was shortened to twenty-five seconds. Since direct heating of the arm is believed to have little effect on the rate of circulation of blood through the skin, and since we have seen that moderate changes in blood flow do not have a marked effect on the threshold, it is clear that the effect of warmth, whether applied indirectly by reflex pathways, or directly by local heating, serves to lower the threshold. The mechanisms in the two types of temperature experiments are not necessarily the same, however, and in all probability are different. Thus, in the local heating experiment, it is likely

that dilating substances are produced by the action of heat on the skin; this is believed by Lewis[2] to be the effect of such procedures. Because of this, a shorter period of ischemia may be expected to elicit an additive effect and so produce the rings of hyperemia. Such a mechanism cannot be imagined in the case of the reflex effects, however.

The final conclusion regarding the mechanism of reactive hyperemia as it is affected by the seasons must be elucidated by further studies. It is clear, however, that enough is now known to make certain that a seasonal variation exists, that the duration of the response may be affected by the flow of blood, and, finally, that the fluctuation in stimulus time results from a seasonal influence on the capacity of the tissues to produce a vasodilating substance, although a variation in the susceptibility of the blood vessels themselves to the same chemical stimulus has not been excluded. There is no evidence in this work to show that such a mechanism may be involved, however, and no seasonal variation has been found in the contractile sensitivity of the cutaneous blood vessels to graded mechanical stimulation.[1]

CONCLUSIONS

1. A method is described whereby the sensitivity of the smallest blood vessels of the skin to graded periods of ischemia may be measured under uniform conditions. The *stimulus time*, measured in seconds, is the minimum period of time that is required to produce three areas of uniform color, size, and sharpness. The *clearing time* is the time required for these areas of reactive hyperemia to disappear. Average values are given for individual subjects under certain conditions and seasons.

2. There was a seasonal variation in the capacity of the skin to give the reactive hyperemia response. Both the stimulation time and the clearing time lengthen progressively in the fall, and reach a high level in December which is maintained until spring. Clearing times shorten before a decrease in the stimulus time begins. The reactive hyperemia response appears to be correlated inversely with outside temperature, and possibly indoor humidity.

3. Attempts were made to ascertain the nature of various factors which might account for the seasonal variation in both stimulus and clearing times. During circulatory stasis the stimulus time is unaffected, but the areas fail to clear. During reactive hyperemia (after release from stasis) the stimulus time is lengthened, but this is shown to be the result of an increase in the rate of washing away of the dilating substance and the consequent need for more of it; this, in turn, requires a longer period of local ischemia.

4. After release from circulatory stasis, a substance is washed away from the occluded area; this lowers the threshold for the reactive hyper-

emia response in remote parts of the body, but it fails, under the conditions of these experiments, to alter blood pressure or heart rate.

5. The role of reflex temperature effects was shown by the fact that there was an elevation of the threshold with cold, and a decrease in threshold with warmth, when the latter were applied to the opposite arm.

6. Direct heating of the skin shortens the stimulus time.

7. In the light of the above considerations, the character of the seasonal variation in reactive hyperemia responsiveness is discussed.

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THE PATHOLOGIC PHYSIOLOGY OF THE CIRCULATION IN ACUTE THROMBOPHLEBITIS AND THE POST-THROMBOTIC SYNDROME

JAMES ROSS VEAL, M.D., AND HUGH HUDSON HUSSEY, M.D.
WASHINGTON, D. C.

THE symptoms of acute thrombophlebitis and the post-thrombotic syndrome are the logical expression of a regular sequence of alterations in the circulation of the involved extremity. The pathologic physiology which underlies these alterations involves all four of the components of the circulatory system, namely, the arterial, venous, lymphatic, and capillary (tissue fluid). The degree to which these alterations are manifest depends principally upon the location and extent of the thrombus. Comprehension of the pathologic physiology is essential in order to treat the disease properly.

ACUTE PHASE OF THROMBOPHLEBITIS

In acute thrombophlebitis, the formation of a thrombus in a principal vein obstructs the flow of blood in this channel. Such obstruction causes damming back of the blood in the vein and its tributaries, with consequent retardation of blood flow and an increase locally in the venous pressure. Accompanying the obstruction, there is vasospasm which affects the arteries as well as the veins. The arterial spasm tends to limit the volume of blood entering the affected extremity and may further diminish the rate of blood flow in the veins. Coincident with the increase in venous pressure, there is stagnation of circulation in the lymphatics. Following these changes in the venous pressure and lymphatic flow, there are outpouring and retention of fluid in the tissue spaces. Along with the phenomena of acute venous occlusion, there is a natural tendency for the venous congestion to be relieved by routes of flow which circumvent the area of obstruction. The efficiency of the collateral circulation depends upon the location and extent of the thrombosis.

The constitutional symptoms which accompany acute thrombophlebitis vary with the virulence of the infecting organisms and the extent of the infection. Thrombophlebitis of a small segment of a superficial vein may produce no constitutional reaction. Involvement of the main venous channels of an extremity usually causes fever ranging from

From the Surgical Service, Gallinger Municipal Hospital, and the Department of Medicine, Georgetown University School of Medicine, Washington, D. C.
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101° to 104° F. Fever may be the first evidence of thrombophlebitis, and it may rise progressively over a period of several days before local signs appear. The fever is often accompanied by chills and other manifestations of toxemia. Leucocytosis and a rapid sedimentation rate usually occur. The duration of the constitutional reaction is greatly influenced by the mode of treatment. The local reaction to acute thrombophlebitis begins with pain and tenderness, particularly along the course of the affected veins. There is rapid swelling of the extremity, with soft, pitting edema. There may be mottled cyanosis, particularly of the digits, and there may be a marked lowering of local skin temperature. The involved veins become firm and cordlike. If the superficial veins are not involved in the process, they may become more prominent and obviously distended. There may be a concomitant lymphangitis, cellulitis, and regional lymphadenitis. In cases of venous thrombosis in which there is no inflammation (phlebothrombosis), constitutional symptoms are absent, but the local circulatory changes are similar to those of acute thrombophlebitis.[1]

The degree of alteration of the venous circulation as a result of thrombophlebitis is primarily dependent on the location and extent of the thrombosis. Although there are numerous tributaries to each main vein, only one or two are large enough to supplant the main vein immediately. It is anatomically obvious that occlusion of a main venous channel and its principal tributary produces more severe obstructive effects than when one of the channels remains patent. For example, ligation of the femoral vein distal to the point of entrance of the saphenous does not produce sufficient obstruction to cause edema. On the other hand, ligation of the femoral vein proximal to the saphenous vein will produce edema of the affected extremity. Similarly, ligation of the axillary vein at a point distal to the site of entrance of the cephalic vein does not produce edema. In cases in which there is obstruction of a main venous channel and its principal tributary, minor tributaries acquire added importance as collateral channels. Therefore, in such cases, as thrombosis further encroaches on additional tributaries, there is an ever-increasing retardation of venous return (Fig. 1). This effect, in turn, increases the likelihood of further propagation of the thrombus.

When a vein is obstructed by thrombosis, there will be retardation of the flow of blood, with consequent congestion of the veins distal to the point of obstruction. The immediate effect of such congestion is a local rise in venous pressure. The amount of rise in venous pressure is inversely proportional to the efficiency of the collateral circulation. As the venous pressure increases, several effects occur almost simultaneously.

The involved veins become distended with blood to the point that the valves are stretched, allowing a reflux of the blood into the tributaries. By means of this reversal of blood flow, distant tributaries may

become collateral vessels in circumventing the area of obstruction. In this way a balance is again obtained between inflow and outflow of blood, but with the venous pressure persistently elevated in many cases. However, this balance is a precarious thing; a slight increase either in the amount of obstruction or of inflowing blood will disturb it, and make necessary a new readjustment at a higher level of venous pressure. The

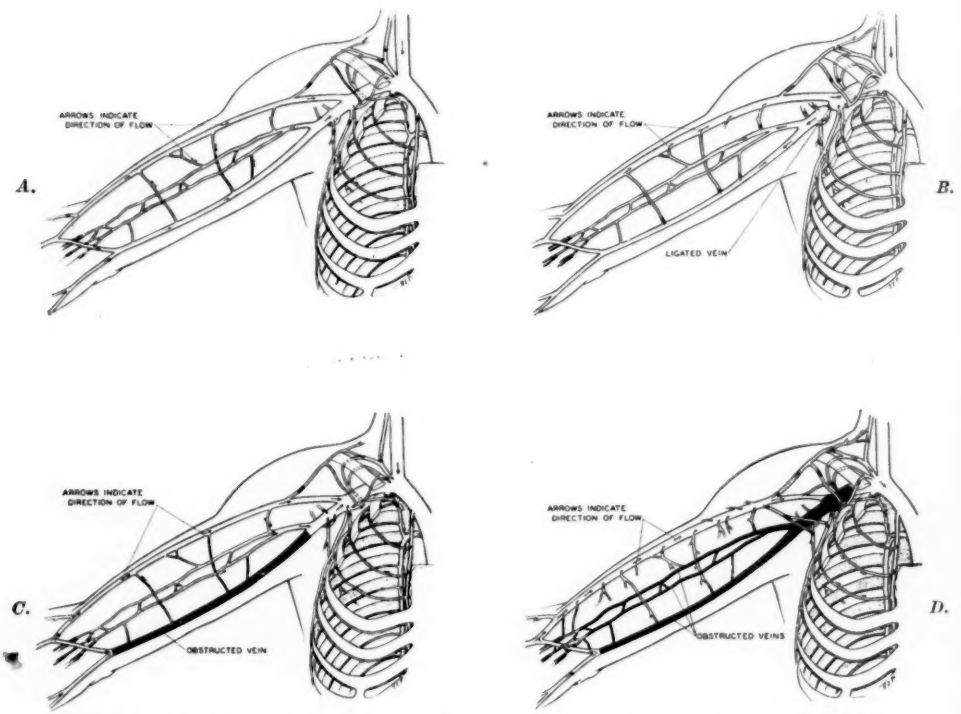

Fig. 1.—*A*, Schema of venous circulation of upper extremity; *B*, schema showing alteration in deep veins caused by ligation of axillary vein at one point; *C*, schema showing immediate compensation of venous return after obstruction of vein distal to points of entrance of main tributaries; *D*, schema showing alteration in circulation after obstruction of entire main venous trunk.

most potent factor which may upset this balance is spread of the thrombosis to such an extent that newly opened collateral channels become obstructed. The onset of menstruation is likely to precipitate spread of the thrombosis. This is apparently caused by the engorgement of the pelvic veins which occurs during this period. The position of the affected extremity is another important factor. Elevation of the extremity will tend to reduce the venous pressure, and dependency will tend to raise it, simply because of changes in hydrostatic pressure in the veins. There are other considerations, which will be discussed later, in connection with the effect of position of the extremity on the circulation. Mechanisms which increase the blood flow to the extremity have a tendency also to increase the venous pressure.

Vasospasm is probably a part of the sequence of events in every case of acute thrombophlebitis.[2, 3] The spasm is not confined to the damaged vessel, but involves other regional vessels, as well, probably through a reflex mechanism. The degree of spasm, however, is variable in different cases and unpredictable in any one case. Generally speaking, the more acute and widespread the thrombophlebitis, the more marked the spasm. The clinical manifestations of the vasospasm include ischemic pain and blanching and coldness of the involved extremity. The spasm may be evanescent, persistent, or recurrent.

The immediate effect of arterial spasm in thrombophlebitis is a marked reduction in the volume and velocity of blood flow in the affected extremity. This produces ischemic pain and tissue anoxemia. Undoubtedly, the most marked spasm usually occurs in the smaller arteries. However, it is not confined to these vessels. Even the main arterial trunk may be occluded by the spasm. In fact, the process may be so severe that gangrene of the extremity results. Indirectly, the slowing of the circulation caused by the spasm adds to the chances of further propagation of the thrombus and the development of emboli. The extent and exact importance of venous spasm in thrombophlebitis are difficult to appraise. In some cases, venous engorgement is obvious in the presence of severe arterial spasm. In other cases, the absence of venous engorgement may denote an accompanying venous spasm. When vasospasm lasts long enough, there may be thrombosis of the small vessels, with far-reaching effects on the ultimate results of the thrombophlebitis.

The arterial spasm may be released spontaneously or by means of certain therapeutic measures. As the acute phase of thrombophlebitis subsides, the tendency to spasm is lessened. The immediate effects of release of arterial spasm include an increase in the volume and velocity of blood flow, relief of anoxemia, and disappearance of ischemic pain. Although release of vasospasm is one of the most important factors in overcoming the immediate effects of thrombophlebitis, it must be remembered that the organic venous obstruction is not relieved. As a matter of fact, the venous pressure rises to a considerable degree (Figs. 4 and 5). This is the logical outcome of increasing the quantity of blood which enters the obstructed venous channels. However, there are certain beneficial results from augmenting the flow of blood in the veins. Increase in the rate of flow lessens the opportunity for extension of the thrombus, and the increase in the venous pressure speeds the development of collateral venous channels. The earlier the spasm is released, the better the chance for limitation of the extent of thrombosis.

The pathogenesis of edema in acute thrombophlebitis is complex. It depends upon a number of distinct factors,[4] all of which, however, are interdependent to some extent. In normal persons the interchange of fluid between the capillaries and tissue spaces is so well regulated

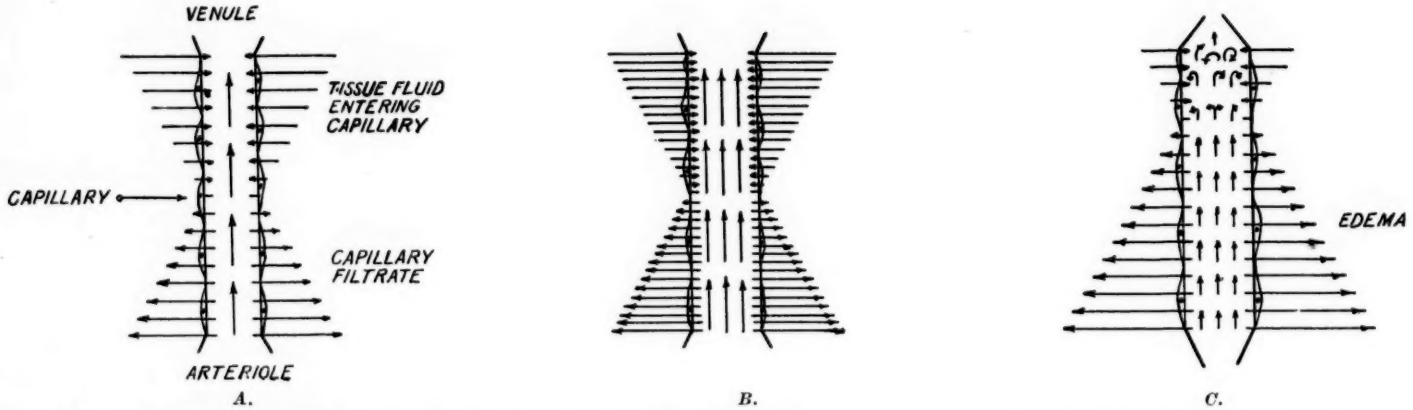

Fig. 2.—Diagram representing exchange of fluid between capillary and tissue spaces with normal circulation and in acute thrombophlebitis. *A*, Normal, resting; *B*, normal, exercise; *C*, venous obstruction with arterial spasm.

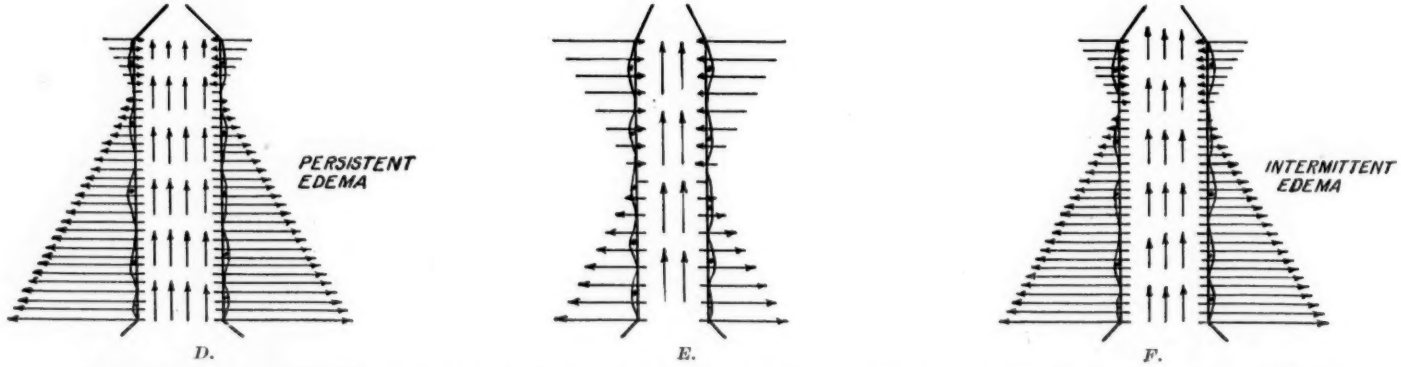

Fig. 3.—Diagram representing exchange of fluid between capillary and tissue spaces in the post-thrombotic syndrome. *A*, Severe persistent venous obstruction; *B*, venous obstruction with compensation while resting; *C*, venous obstruction with decompensation during exercise.

that the volume of tissue fluid is remarkably constant. Even during exercise there is little change except an increase in the velocity of fluid exchange (Fig. 2*A* and *B*). In thrombophlebitis the prime factor in causing edema is elevation of the venous pressure,[5] for, when the initial readjustment of the circulation to obstruction of the veins does not result in a persistent elevation of the venous pressure, edema will not develop. On the other hand, when there is persistent and sufficient elevation of the venous pressure, increased capillary pressure results, and there is, consequently, a tendency for fluid to accumulate in the tissue spaces (Fig. 3*D*). Another important factor in the development of edema, particularly during the acute stage of thrombophlebitis, is local anoxemia of the tissues. At the onset of the venous obstruction there is an abrupt retardation of blood flow through the veins. Simultaneously, there may be arterial spasm which reduces the volume of blood flow and tends therefore to slow the current still further (Fig. 2*C*). During this stage, samples of venous blood invariably show a marked lowering of oxygen content.[6] As a consequence of such anoxemia, capillary permeability is increased, and there is an abnormal outpouring of fluid into the tissue spaces. There is some evidence, also, that anoxemia engenders an accumulation of tissue metabolites which increase the water-holding capacity of the tissue fluid. The degree and duration of the anoxemia depend upon the severity of the venous obstruction and the amount of arterial spasm. With the development of venous collaterals and release of arterial spasm, anoxemia tends to be relieved. A third factor in the pathogenesis of edema in acute thrombophlebitis is slowing of the lymphatic circulation. In the presence of venous obstruction and slowing of the venous flow, the lymphatic vessels become the main potential route of egress for the tissue fluid. Therefore, if flow by this route also is retarded, the tendency to edema formation is aggravated. Unfortunately, flow in the lymphatics is apparently directly dependent on an intact venous circulation, so that conditions which impede venous blood flow overburden the lymphatic circulation. Dependency of the affected part, of course, may cause the flow in the lymphatics to be further impeded. An increase in the volume of fluid in the lymphatic vessels probably causes them to become distended, so that their valves are incompetent. This process may be of such degree that the lymphatic circulation becomes completely decompensated. Apparently, the superficial lymphatic vessels are mainly affected. The ever-present tonus of the muscles continues to promote emptying of the deep lymphatics. It has been shown that the amplitude of the arterial pulse also influences lymphatic flow.[7-9] During the phase of arterial spasm, the effect of the arterial pulse on lymphatic flow is diminished. When vasospasm is released, one factor which contributes to lymphatic stagnation is withdrawn. It should be emphasized at this point that the lymphatic obstruction of acute thrombophlebitis is usually func-

tional and is not caused by the kind of occlusion of lymphatic vessels which may develop in the post-thrombotic syndrome. Therefore, in the earlier stage, the lymphatic obstruction is usually a reversible process; normal lymphatic circulation may be restored. In many cases, there are regional lymphangitis and lymphadenitis. These are confined to the lymphatics adjacent to the portions of the veins involved in the acute inflammatory process and to the lymph nodes draining the region. However, the regional lymphangitis and lymphadenitis probably have little effect on the lymphatic circulation in general.

It is during the acute stage of thrombophlebitis, before organization of the thrombus has begun, that embolism may occur. In some cases the thrombus may be attached firmly to the endothelium of the vein along its whole length. In other cases the thrombus is attached only in part or loosely. It is in this latter type of case that the danger of embolism is greatest.[10] Propagation of a thrombus from one vein into a larger vein, or from a segment of vein of a smaller caliber into another segment of larger caliber, predisposes to embolism. Such an extension of the clot is most likely to occur during the acute phase of thrombophlebitis, when blood flow is slowest as the result of vasospasm and venous obstruction.

POST-THROMBOTIC SYNDROME

The termination of the acute phase of thrombophlebitis may be recognized by disappearance of constitutional symptoms and local inflammatory changes. At the same time, organization of the thrombus begins. The thrombus certainly is not reabsorbed in the majority of cases. The vein tends to undergo recanalization, but this process is seldom sufficient in itself to restore normal circulation. When the acute phase has passed, the immediate results depend upon the degree to which the altered circulation has been corrected. If the thrombophlebitis has been confined to an unimportant vein or to a segment of a main vein for which adequate collateral vessels are available, there will be no permanent, significant, circulatory changes. On the other hand, if the thrombus is lodged in a main venous channel in such a location that some or all of the principal tributary veins are also obstructed, certain permanent circulatory changes will remain. These changes constitute the post-thrombotic syndrome.

The manifestations of the post-thrombotic syndrome are a logical result of the circulatory alterations. As in the acute stage, these alterations involve all four of the components of the circulation. The changes in the arterial component, however, seem to be of relatively minor importance. With subsidence of the acute phase, arterial spasm apparently disappears completely. Possibly there is even persistent dilatation of the arterioles and capillaries, although the evidence for this is incomplete. The state of the venous circulation in this stage again depends

upon the degree of obstruction and the development of collaterals. Whereas, in the acute phase of thrombophlebitis, the impairment of lymphatic circulation usually is purely functional, in the post-thrombotic syndrome an organic factor may be added. Edema is usually a prominent symptom and may be persistent or may appear only with exercise or dependency of the limb. The edema may be of the soft, pitting type or may be firm and nonpitting. Additional consequences of the persistently altered circulation in the involved extremity include recurrent thrombophlebitis, the development of varicosities, recurrent local cellulitis and lymphangitis, and a tendency to the formation of indolent ulcers.

After the obstruction of the veins, in order that the affected extremity may resume its normal function, there must be an adequate inflow of arterial blood and a prompt and adequate venous outflow. In the post-thrombotic syndrome the arterial inflow is probably adequate at all times and under varying conditions of activity. The efficiency of the venous circulation necessarily depends upon the degree and extent of venous obstruction and the competency of the collateral veins. In many cases the collateral vessels are sufficient in number, size, and distribution to compensate for the venous obstruction while the affected extremity is at rest (Fig. 3*E*). In these cases the venous pressure is normal, or at least below the level at which edema is produced. However, during exercise the collateral veins may be incapable of carrying away the additional blood brought in through the arteries.[11] The veins therefore become overfilled, and the venous pressure rises (Figs. 4 and 6). If the increment in venous pressure is great enough, there will be excessive filtration of fluid into the tissue spaces, and reabsorption of this fluid will not take place at a normal rate. If this state lasts long enough, there will be a sufficient accumulation of fluid in the tissue spaces to produce edema (Fig. 3*F*). When a state of inactivity is resumed, the venous circulation again serves adequately for the arterial inflow, and edema subsides. Similar changes in the venous pressure may result from placing the affected extremity in a dependent position. In women there is often an increase in the edema just before menstruation. This is frequently associated with pain in the affected extremity. We do not know whether or not this type of premenstrual edema is related to changes in the venous pressure. A similar tendency to aggravation of the symptoms of the post-thrombotic syndrome is observed during pregnancy,[12] and is apparently due to an increase in local venous pressure. It must be remembered that the collateral channels usually develop through superficial veins.[13] In such veins, the impetus imparted to the flow of blood by muscle tonus is lacking, and the squeezing action of muscular exercise is ineffectual. The newly developed collaterals are usually long, tortuous, and devoid of valves. All of these factors, plus the ef-

fect of hydrostatic pressure, combine to impede the venous outflow from the dependent extremity. Since arterial inflow continues, an abnormal rise in venous pressure results. In other cases of the post-thrombotic syndrome, the collateral vessels are insufficient in size and number to compensate for the venous obstruction, even during rest in a favorable position. In such cases, because of the persistently high venous pressure, there is edema even during rest (Fig. 3*D*). This is aggravated by lowering the affected extremity or by exercise. Due to the congestion of the veins as the result of these factors, recurrent thrombophlebitis is more common than in normal veins.

A varicose state frequently, but not invariably, follows thrombophlebitis of the principal veins of the upper or lower extremities. When obstruction to the principal vein is in such a location and of such a degree that the pressure is increased in the superficial venous tributaries, they undergo dilatation, their valves become incompetent, and a reflux of blood flow is permitted. This process may extend to minor tributaries which are quite distant from the point of obstruction. The process is a gradual one, and varicose veins may not become clinically obvious until several months after the disappearance of the acute phase of the thrombophlebitis. The communicating veins between the superficial and deep veins also undergo dilatation, and their valves become incompetent. When this state of dilatation of the superficial veins due to high venous pressure is allowed to endure long enough, organic changes ensue in the veins and their valves.[14] These structural changes are irreversible, so that the varicose state of the veins persists, even though the venous pressure later becomes lowered as a result of further development of collateral circulation, or of recanalization of the vein. Another factor which influences the development of superficial varicosities is the anatomic distribution of the veins. In some normal persons the superficial veins are relatively few and relatively unimportant as channels for venous return. In such persons the opportunity for development of superficial varicosities is necessarily limited. In others the superficial veins are numerous and carry a large volume of blood. In these, large numbers of varicose veins may readily develop. Protection of the superficial venous system against dilatation may limit or prevent the development of a varicose state.

In the post-thrombotic syndrome, the importance of the lymphatic circulation in the development of symptoms is greater than in the acute phase of thrombophlebitis. In the acute phase there is a tendency to stagnation of fluid in the lymphatic vessels of the whole extremity. This is not due so much to the lymphadenitis and lymphangitis in the region of the inflamed vein. For example, acute inguinal lymphangitis and lymphadenitis often exist without producing any evidence of peripheral lymphatic obstruction. The lymphatic stagnation which accom-

panies acute thrombophlebitis is primarily due to retardation of venous blood flow and increase in venous pressure. These two factors cause an increase in the amount of tissue fluid, as mentioned above, and, consequently, the entire lymphatic system of the extremity becomes overfilled. If the venous congestion is promptly relieved, there is immediate restoration of the normal lymphatic circulation. On the other hand, if the venous pressure remains persistently elevated, structural changes similar to those in the superficial veins occur in the lymphatic vessels. Therefore, there is a kind of chronic varicose state of the lymphatic vessels, and this becomes irreversible. The walls and valves of the vessels are thickened, and there is perilymphatic fibrosis. These changes are permanent and are little affected by the development of an adequate collateral venous circulation. In other words, lymphatic stasis may persist, although the venous congestion, which originally initiated the lymphatic stasis, may have been relieved. When this state obtains, there is an increased susceptibility to infection, and frequent attacks of cellulitis and widespread lymphangitis occur. They are accompanied by fever, leucocytosis, pain, evidence of superficial inflammation in the extremity, and regional lymphadenitis. Such attacks aggravate the organic changes which are responsible for the lymphatic obstruction. With the organic lymphatic obstruction which characterizes many cases of the post-thrombotic syndrome, the skin of the affected extremity becomes thick and brawny, and does not pit on pressure. If appropriate measures are employed before the stage of organic lymphatic obstruction has been reached, a pitiful and almost hopeless state of elephantiasis usually can be prevented.

One of the more serious common consequences of the post-thrombotic syndrome is the development of ulceration in the affected extremity. Such ulcers usually occur in the region of the lower one-third of the leg, where the arterial blood supply is poorest. Occasionally they seem to occur spontaneously, but usually follow some form of local trauma, cellulitis due to acute infection, or recurrent thrombophlebitis. Once the ulcer appears, it tends to spread slowly and to become indolent. Ulceration of this type may develop whether or not varicose veins are present. The pathogenesis of the ulceration is not exactly unknown.

SUGGESTIONS ON THERAPY

We wish to emphasize that the prime consideration in acute thrombophlebitis is not recognition of the fact that a clot has formed in a vein, but the fact that all elements of the circulation in the affected extremity are altered as a result of the venous occlusion. The degree of this alteration will, of course, depend upon the location and extent of the thrombus and the severity of the local inflammatory process in the veins. The importance of this viewpoint in the treatment of acute

thrombophlebitis becomes apparent as soon as we realize that little or nothing can be done to influence the blood clot which has already formed. The only exception to this statement is that in certain cases it is possible to minimize the danger of embolism by ligation of the vein above the thrombus. The treatment of the disease, in general, must be directed to the relief of those changes which take place in all components of the circulation in the affected extremity.

Therapy should be primarily intended to correct the stagnation of blood and lymph flow in the involved extremity. By this means it may be possible to prevent propagation of the thrombus. There are three important measures which should be applied for the alleviation of the stagnation. They are, in the order of their importance, release of vasospasm, elevation of the extremity, and active movement of the extremity.

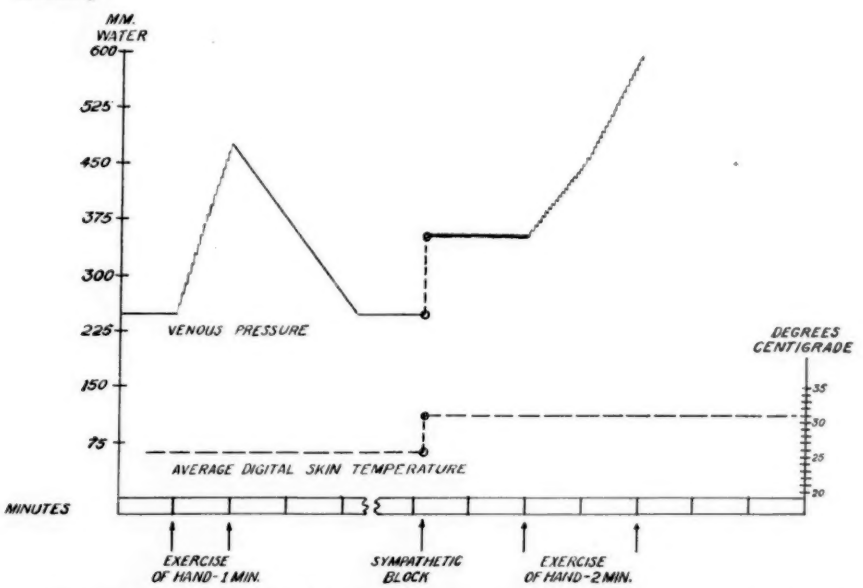

Fig. 4.—Acute thrombophlebitis of axillary and subclavian veins. Note abnormal elevation of venous pressure during rest, with prompt rise during exercise. Note the effect of sympathetic block on venous pressure and skin temperature.

Release of vasospasm and promotion of vasodilation produce a great increase in the rate and volume of blood flow in the arteries and capillaries.[15] The improvement in the capillary circulation tends to relieve anoxemia, and thereby removes one of the factors which influence the abnormal filtration of fluid into the tissue spaces. The increase in the amount of blood entering the veins through the dilated arteries and capillaries throws an added load on the already overfilled veins. As a result, the venous pressure actually rises, but the volume of flow through the veins is increased, mainly because of the increase in vis a tergo from the dilated capillary bed (Figs. 4 and 5). Possibly some improvement

results from the release of venous spasm. There is probably also an increase in lymphatic flow because of the augmentation in the amplitude of arterial pulsations which results from vasodilation. Release of vasospasm can be obtained in several ways, but not necessarily to the same degree in each. One of the measures used to overcome vasospasm is that of raising the body temperature to a febrile level. It is interesting that, in some cases of acute thrombophlebitis, local vasospasm persists

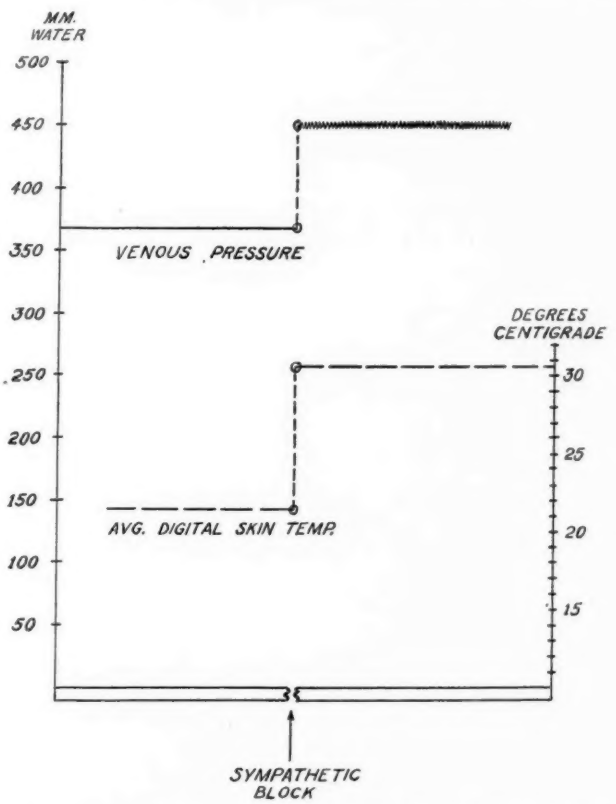

Fig. 5.—Acute iliofemoral thrombophlebitis. Note high initial venous pressure and low skin temperature. Sympathetic block produced increase in venous pressure and rise in skin temperature.

in spite of a rise in body temperature to 103° or 104°. In such cases, a further increase of body temperature by artificial means does not seem warranted. Some other measure which acts directly on the local spasm must be instituted. It is to be emphasized that complete release must be secured. If one measure does not suffice, additional procedures must be employed (Fig. 7). It must also be emphasized that the release of vasospasm, a return of the patient's temperature to normal, and the disappearance of edema while the patient is at rest in bed cannot be accepted as summary evidence that the derangement of the circulation has been completely corrected.

Elevation of the affected extremity above the level of the heart tends to remove the factor of hydrostatic pressure. Emptying of the veins and lymphatics is thereby enhanced.

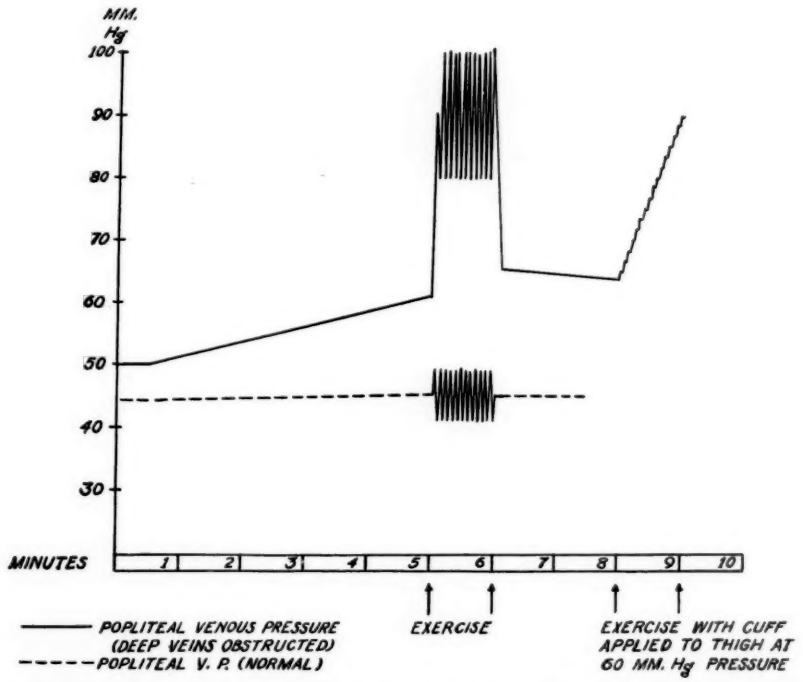

Fig. 6.—Post-thrombotic stage of iliofemoral thrombophlebitis. Note the extreme elevation in venous pressure on the affected side during exercise as compared to the normal fluctuation on the unaffected side. The extreme oscillations in venous pressure on the obstructed side during exercise were apparently due to incompetency of the communicating veins, as demonstrated by disappearance of the wide excursions when the superficial veins were occluded by means of a tourniquet.

Active motion of the extremity by the patient promotes emptying of the lymphatics and veins. Furthermore, it improves the circulation by increasing the rate and volume of arterial blood flow. The danger of embolism as a result of dislodgment of a portion of a thrombus caused by movement of the affected extremity is often postulated. In our own experience, the opposite has been true. Prolonged immobility seems to favor extension of the thrombus beyond its fixed point in the area of phlebitis, and, since the extended portion is not fixed to the vein wall, it may be dislodged.

Pain in thrombophlebitis is of two types. There is pain at the site of the thrombosed veins which is due to the local inflammatory reaction. There is also general pain in the affected extremity which is probably due to anoxemia caused by vasospasm. The latter type of pain is promptly banished when the anoxemia is relieved by measures which produce vasodilation.

The relief of edema is accomplished in part by the same measures which tend to overcome stagnation of blood and lymph flow, namely, release of vasospasm, with consequent elimination of anoxemia, and elevation and active movement of the extremity. Nature soon comes to the aid of the physician by developing collateral venous channels.

When the proper measures, as mentioned above, are instituted, the local thrombophlebitis is limited, and usually the constitutional symptoms rapidly subside. Occasionally the inflammatory process becomes suppurative, in which case the systemic symptoms of inflammation are correspondingly protracted.

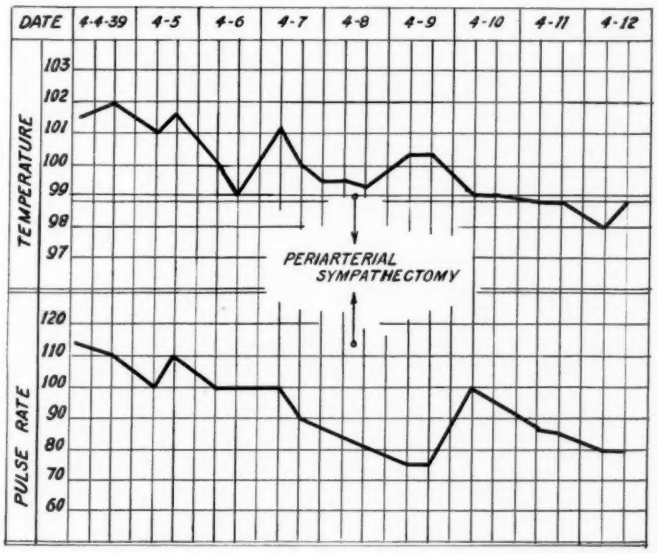

Fig. 7.—Post-partum iliofemoral thrombophlebitis. Acute pain in region of lower part of thigh and knee, cyanosis of entire extremity, and absence of femoral pulsation simulating arterial embolism. Exploration of femoral vessels revealed thrombophlebitis, with spasm of artery. Periarterial sympathectomy immediately restored pulsations and relieved ischemic pain.

It is almost unnecessary to point out the importance of early treatment of acute thrombophlebitis. When stagnation of venous flow is prolonged, the opportunity for propagation of the thrombus is increased, and the circulatory changes are consequently more severe. In turn, the possibilities for restoration of a normal circulation are more limited.

Once the post-thrombotic stage of acute thrombophlebitis has been reached, the attitude of patient and physician toward treatment of the affected extremity too often becomes apathetic. Many times the physician expresses his attitude toward the disease by complete inactivity. He assumes that the patient is doomed to all of the undesirable complications which we have described above. Frequently the process is relegated to the status of those conditions which can be observed while "nature takes its course." Although the importance of natural

processes of repair cannot be underestimated, it is nevertheless true that a great deal of assistance to recovery can be given, and that, by proper treatment, based on a knowledge of the character of the circulatory changes, many of the undesirable complications can be minimized or wholly prevented.

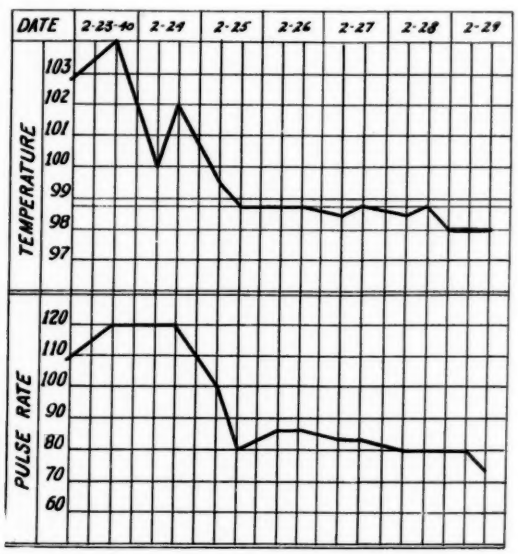

Fig. 8.—Post-thrombotic syndrome, with recurrent cellulitis. Lymphangitis, and lymphadenitis. Severe constitutional and local reaction. Treatment by rest in bed, warm compresses, and sulfanilamide.

Treatment of the post-thrombotic syndrome should begin before the patient with acute thrombophlebitis is allowed to resume his normal activities. The most important therapeutic measures are those which encourage the development of a collateral channel and tend to prevent overfilling of the superficial veins and lymphatics. These measures should include the use of pressure bandages of some type. The bandage should be applied with a pressure which is sufficient only to compress the superficial veins and lymphatics. A bandage which impedes arterial circulation even slightly is to be condemned. On the other hand, any type of bandage which does not produce a uniform compression of the superficial vessels is useless and may be harmful. In our experience the most efficient type of bandage is a properly fitted elastic stocking. By this means, the superficial veins and lymphatics are prevented from becoming abnormally dilated, and edema is limited. Prevention of dilatation of the superficial veins encourages the development of deep collateral vessels. This is desirable because the deep veins carry blood more efficiently during muscular activity and do not tend to become varicose. The same is true with respect to the lymphatics.

Recurrent thrombophlebitis, cellulitis, and lymphangitis are common in an extremity in which the superficial vessels are allowed to become dilated. These complications, as well as edema, predispose to the development of ulceration. Therefore, if the superficial vessels are prevented from becoming dilated, there is less likelihood of recurrent thrombophlebitis, cellulitis, lymphangitis, and ulceration. Treatment of the attack of cellulitis and lymphangitis by rest in bed, elevation of the extremity, the local application of moist, warm compresses, and the administration of sulfanilamide often gives spectacular results (Figs. 8 and 9).

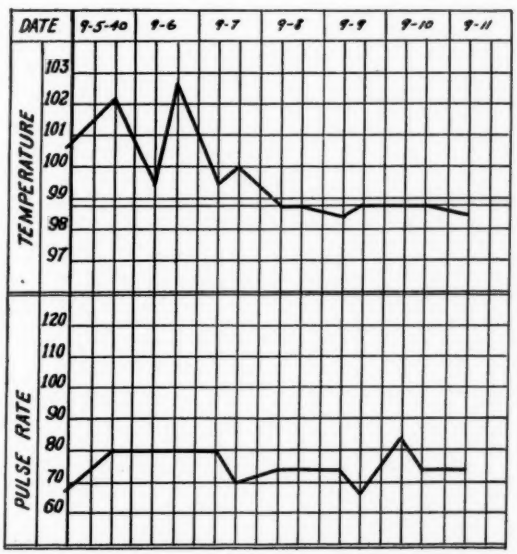

Fig. 9.—Post-thrombotic syndrome, with recurrent cellulitis and lymphangitis. Mild constitutional and local reaction. Treatment by rest in bed, warm compresses, and sulfanilamide.

Active surgical measures which involve any part of the venous circulation have no place in the therapy of the post-thrombotic syndrome as long as the venous pressure in the affected extremity is abnormally high at rest, or becomes abnormally high during exercise (Fig. 6). As a matter of fact, surgical interference with the veins under these conditions is a form of undesirable meddling.

The patient must be made to understand the objects of therapy in the post-thrombotic syndrome. He must realize that the length of time required for the accomplishment of these objects is necessarily variable and unpredictable, but that in any case it will be prolonged over a period of months, or even years. The physician must realize that treatment must be continued as long as there is any evidence of derangement of the circulation in the arteries, veins, lymphatics, and tissue spaces.

CONCLUSIONS

In acute thrombophlebitis and the post-thrombotic syndrome all components of the circulatory system in the affected extremity are implicated in the production of symptoms. The degree to which each component is affected varies with the stage of the disease. In a larger sense, the effects of the circulatory involvement depend fundamentally upon the location and extent of the thrombotic process. Treatment of the effects of thrombophlebitis and the post-thrombotic syndrome can be logical only when the nature of the alterations in the physiology of the various components of the circulation is thoroughly understood.

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DISCUSSION

DR. A. W. DURYEE, New York, N. Y.—I should like to compliment Dr. Veal and Dr. Hussey on their excellent presentation. I should also like to suggest that there are perhaps two other factors that influence the development of thrombophlebitis, especially in the upper extremities, which must be considered in the treatment of the post-thrombophlebitic state.

One of these factors is the variation in development of the venous system. Those who have done many venograms realize that the arrangement of the veins in the arms and legs varies tremendously.

Another factor of importance in the upper extremities is that muscle abnormalities and bone abnormalities in the region of the shoulder may obstruct venous return. One may find, in an apparently normal person, an elevated venous pressure which can be explained only by muscle or bone pressure on the veins. If any surgical operation is performed on these patients, especially in the post-thrombophlebitic stage, the procedure which is indicated is release of the pressure by scalenectomy or some similar operation.

DR. GEZA DE TAKATS, Chicago.—In addition to the therapeutic measures which Dr. Hussey has discussed, I should like to mention briefly two very simple methods which have proved to be of great help to us in the management of acute thrombophlebitic edema. One is the use of diuretics. As you know, if edema is allowed to persist, a state of thrombophlebitic induration may develop.

The other measure which we have used to great advantage in the treatment of periphlebitis and lymphangitis is small doses of roentgen therapy over the affected area, usually in the iliofemoral regions, but sometimes over the calf muscles.

There is one more point I should like to emphasize in connection with the late sequelae of thrombophlebitic edema, and that is that the interference with the circulation is due not only to the fact that persistent, chronic vasospasm may be present, or that veins may be occluded, or that lymphatic destruction exists, but to the fact that such a potent reflux of blood occurs in the standing position that it is almost impossible to treat.

Before this Society I had the pleasure of discussing a paper by Dr. Edwards, who showed that every time larger veins are occluded the valves are destroyed, and, even if canalization occurs, the valves become insufficient. We have seen patients with beginning of thrombosis who came back later showing not as much deep venous obstruction as deep venous insufficiency; that is to say, a great amount of blood would fill up the lower extremity because the valves in the iliac or femoral veins were incompetent. We have been unable up to the present time to find any solution of the therapeutic problem, except by bandaging.

DR. NORMAN E. FREEMAN, Philadelphia.—I believe Dr. Veal and Dr. Hussey have done a splendid piece of work in bringing together these facts on venous obstruction. There are two aspects of this question which I should like to take up very briefly.

The first is the question: Is there arterial spasm in the acute stages of thrombophlebitis? I believe that, in a small number of cases, there is actually enough arterial spasm to produce arterial insufficiency. However, in my experience, the general picture of acute thrombophlebitis, especially the mild type, not the massive iliofemoral thrombosis, shows an increase of blood flow to the part. There is a rise in skin temperature. There is an increase in oscillations, and, as Dr. De Takats has pointed out, the sole of the foot on the involved side is warmer than that on the normal side.

Linton, last year, at the Vascular Section meetings, presented an interesting experimental demonstration of the fact that obstruction of the venous return would actually increase the arterial flow into the affected part. There are controversies as to the mechanism of this increase in blood flow which is associated with venous occlusion, but his experimental demonstration fits in with our clinical observation that there are a rise in skin temperature and an increase in the oscillations on the affected side.

As far as treatment is concerned, we realize that simple ligation of a vein, even the femoral vein, is accompanied by less deleterious and less disastrous results than thrombophlebitis. In one of my cases, this thrombophlebitis finally went on to gangrene. At the time the leg was amputated it was found that there was extensive arborization thrombosis of the venous radicals, extending all the way down the femoral to the popliteal vein. In the branches of these veins there was extension of the thrombotic process.

The amount of disability that patients will suffer in the postphlebitic stage does depend to a certain extent upon the amount of thrombosis which takes place, and so I feel that the efforts that Dr. Veal has mentioned, which are designed to limit the thrombosis, are of great significance.

One additional procedure in the treatment of acute thrombophlebitis may be worth while, namely, tight compression of the involved extremities with elastic bandages while the patients are in bed immediately after the acute thrombophlebitis has taken place. It may be that in this way we can prevent the arborization thrombosis.

There was a question in our minds as to whether it was advisable to limit the return circulation still further by applying pressure to the superficial veins, but the fact that there was evidence of increased circulation, as shown by skin temperature and by the oscillometer, suggested that there were collateral channels available when the main return channel was blocked, for the increase in temperature must mean that there was more blood coming out of the leg, as well as more blood going into it. We knew that, under such circumstances, the venous pressure would rise until it met diastolic pressure, and therefore we did not apply enough pressure to occlude the arterial flow, for we realized that there was available venous collateral circulation to take the blood back.

In closing, I should like to say a word about the use of heparin, which has not been mentioned today. Dr. Gordon Murray, in Toronto, has employed it routinely in his cases of severe iliofemoral thrombophlebitis. We have had experience with it in about twenty-five cases, and we feel that it does help to put a stop to the arborization thrombotic process, and so may help to cut short the severe disability which these patients experience in after months.

Dr. Edgar A. Hines, Rochester, Minn.—It is my impression that the sulfonamides have not been of very great value in the treatment of acute thrombophlebitis, particularly in postoperative thrombophlebitis. I have observed a number of cases in which thrombophlebitis has developed during adequate sulfonamide therapy.

Would Dr. Hussey comment regarding this type of therapy? I noted from his slides that he had given some of his patients sulfanilamide.

Dr. J. Ross Veal.—With respect to the remarks of Dr. de Takats, we have had no experience with roentgen therapy and diuretics in cases of acute edema in thrombophlebitis.

Dr. Freeman mentioned elastic bandages. That brings up one of the most important points in the treatment of thrombophlebitis. So many types of bandages are on the market that I am afraid most of them are used improperly. Many patients who come into the hospital wearing very tightly applied, so-called "Ace" bandages, or other kinds of bandages which contain a compound that sticks to the skin, have ulcerations under the bandages. We feel that bandages should be just sufficiently tight (uniformly over the whole extremity) to compress the veins and

superficial lymphatics, without interfering with the arterial blood supply. Tight bandages do serious harm, and loose bandages have no beneficial effect whatsoever.

Dr. Freeman mentioned skin temperatures in acute thrombophlebitis. The striking thing about this is that the patients differ greatly; one will have a cold extremity, and another may have a warm extremity. Why this is so we do not know, but, in our experience, there is usually some evidence of vasospasm during the acute phase of thrombophlebitis, and we believe that this depends upon the degree or extent of thrombosis of the large veins.

Dr. Hines mentioned sulfanilamide. We have found that this drug does little good in the acute stages of thrombophlebitis, but it works very well in the acute post-thrombotic stages.

BLOOD PRESSURE STUDIES ON NEGRO AND WHITE MEN AND WOMEN LIVING IN THE VIRGIN ISLANDS OF THE UNITED STATES

G. M. Saunders, M.D., and Huldah Bancroft, A.B., M.A.
Cleveland, Ohio

DURING 1939 and 1940, clinical examinations, including blood pressure observations, of a large proportion of the population of the Virgin Islands were made. It is the purpose of this article to analyze the blood pressure observations and to compare them with studies made in the United States and elsewhere.

DESCRIPTION OF AREA

The Virgin Islands of the United States are situated in the Caribbean Sea, about 40 miles east of Puerto Rico. There are three main islands in the group, namely, St. Thomas and St. John, which lie together between Puerto Rico and the British Virgin Islands, and St. Croix, which is about 40 miles south of St. Thomas. The climate, which may be described as subtropical, is agreeable and pleasant, with temperatures ranging from 68° F. to 92° F., and a mean annual temperature of about 80° F. The average rainfall amounts to approximately 46 inches a year, but frequent and severe droughts occur. The inhabitants number nearly 25,000, of whom only 700 live on St. John; the remainder are about equally divided between St. Thomas and St. Croix. About 70 per cent are negroes; 20 per cent are colored, and the remaining 10 per cent are white or Puerto Ricans, most of whom are of mixed Indian, white, and negro blood. General health conditions in the Virgin Islands compare very favorably with the other West Indies islands, and tropical diseases are rare except for occasional cases of malaria and dysentery, and filariasis, which is prevalent in St. Croix.[1] Yaws does not occur, but syphilis is present in about 16 per cent of the entire population, i.e., in 18 per cent of the negroes, and 4 per cent of the whites.[2] Because the islands are very poor, and do not yield agricultural products in any quantity, the general diet is inadequate in kind, although the amount seems sufficient to keep the majority of the people well nourished. As a result, the general health suffers, and deficiency diseases are relatively common, especially pellagra and skin and eye changes due to lack of vitamin A.

The observations upon which this study is based were conducted under the auspices and with the support of the Leonard Wood Memorial and were aided by a W.P.A. project.

Received for publication Aug. 2, 1941.

METHODS OF STUDY

In St. Thomas, during 1939, the entire population of nearly 11,000 was included in a house-to-house census, and about 7,200 were examined in the clinic. In St. Croix, during 1940, a census was taken of a rural population group, numbering about 5,100, of whom nearly 4,800 were examined. In St. Thomas, blood pressure observations were made routinely on all examined persons who had reached the age of 15 years; whereas, in St. Croix, blood pressure readings were made only as time permitted, and without selection as to age or physical condition. The combined group from the two islands on whom readings were made probably represents a good random sample of the entire population. All readings were made with a standard mercury sphygmomanometer, with the patient either sitting in a chair with the arm resting on a table about breast-high, or in a reclining position. Readings were made several minutes after the patient had entered the examining room and a brief medical history had been taken. The level of the appearance of the first sound was recorded as the systolic pressure, and the change in sound as the diastolic pressure. Readings were frequently repeated if they appeared to be unusual.

Because the colored group was small and showed little difference in blood pressure, they are included with the negroes. The white population is considered separately because their blood pressure readings were consistently different from those of the negroes. The small group of Puerto Ricans is not included. Blood pressure observations were recorded on 4,913 persons (4,374 negroes and 539 whites), representing more than 50 per cent of the enumerated population over 15 years old.

OBSERVATIONS

Systolic Blood Pressure.—The mean systolic pressure of negroes and whites, by sex and age, is recorded in Tables I and II, and the systolic pressure of negroes is shown in Fig. 1. The level for male negroes rose steadily, with age, from 120 mm. between the ages of 15 and 19 years to 164 mm. among those who were 65 to 69 years old, after which there was a decrease. For females the level was essentially the same as that of males up to the age of 35 years, after which it began to increase more rapidly than in males; it reached a peak of 184 mm. between the ages of 70 and 75 years, and then decreased. The standard deviation increased in both sexes from a level of about 14 mm. among the younger persons to more than 30 mm. in old age, which is indicative of the greater range of readings with advancing age. The mean for all ages for males was 138.62 ± 0.68; and for females it was 147.05 ± 0.68. After standardization for age, the mean for males became 138.92, and, for females, 146.10, which is a difference of 7.18 ± 0.96. This indicates that, among negroes, females have a significantly higher mean systolic blood pressure than males.

Among white persons, the systolic blood pressure likewise increased with age. The mean, standardized for age, was 126.51 mm. for males and 133.30 mm. for females, which is a difference of 6.79 mm. $\pm$ 1.99. Here, again, the general average was significantly higher in females than in males. A comparison of mean systolic pressure, standardized for age, reveals that the pressure for both sexes among negroes was

considerably higher than among whites; male negroes had a mean systolic pressure 12.41 mm. higher than male whites; and female negroes had a mean systolic pressure 12.80 mm. higher than female whites.

TABLE I

MEAN SYSTOLIC BLOOD PRESSURE OF NEGROES, BY SEX AND AGE

AGE (YEARS)	MALES			FEMALES		
	NO.	PRESSURE (MM.)	STANDARD DEVIATION OF SAMPLE	NO.	PRESSURE (MM.)	STANDARD DEVIATION OF SAMPLE
15-19	240	120.39	17.21	315	123.14	14.28
20-24	268	123.48	14.74	287	123.27	14.41
25-29	222	128.72	19.93	274	126.41	16.10
30-34	155	131.47	20.00	214	131.22	20.06
35-39	146	132.29	22.56	216	141.21	26.85
40-44	122	143.44	27.07	216	146.66	28.75
45-49	139	149.77	31.89	209	159.34	33.73
50-54	133	149.76	32.32	220	168.50	42.67
55-59	135	158.94	35.57	199	173.83	33.61
60-64	126	160.63	33.25	143	177.88	32.25
65-69	81	164.04	29.90	102	182.50	31.79
70-74	39	160.83	31.08	67	183.91	36.69
75-79	26	146.35	36.25	40	177.12	35.43
Over 80	17	163.09	30.71	23	166.19	24.20
Total	1,849	138.62	29.34	2,525	147.05	34.14
Mean (standardized for age)		138.92			146.10	

TABLE II

MEAN SYSTOLIC BLOOD PRESSURE OF WHITE PERSONS, BY SEX AND AGE

AGE (YEARS)	MALES			FEMALES		
	NO.	PRESSURE (MM.)	STANDARD DEVIATION OF SAMPLE	NO.	PRESSURE (MM.)	STANDARD DEVIATION OF SAMPLE
15-19	39	117.65	12.20	22	123.87	10.89
20-24	39	118.15	11.50	30	120.17	9.10
25-29	33	124.15	13.10	28	124.83	14.30
30-34	36	124.15	15.55	33	124.32	11.54
35-39	37	133.20	18.50	23	126.64	14.64
40-44	29	131.30	17.85	25	125.70	13.41
45-49	20	138.75	25.20	30	137.00	19.25
50-54	25	143.50	28.92	17	141.33	25.70
55-59	17	151.90	32.67	14	155.00	22.66
60-64	7	163.95	27.83	19	165.65	35.59
65-69	8	149.40	29.12			
Over 70				8	163.75	25.58
Total	290	130.30	22.80	249	133.03	23.11
Mean (standardized for age)		126.51			133.30	

Although the mean systolic pressure is valuable, it may be unduly weighted by a few very high or very low readings. Also important is the percentage of persons with blood pressures above one level and below another. We have arbitrarily used 150 mm. and 110 mm. for the upper

and lower levels because we were able to find comparative studies in which these figures had been chosen. Table III and Figs. 2 and 3 show the percentage of negroes of both sexes with a systolic blood pressure of 150 mm. or more, or less than 110 mm. The proportion with high blood pressures increases very markedly, with age, from a low to a very high level, with a male preponderance after 50. When only pressures below 110 mm. are considered, the reverse is true, namely, the proportion

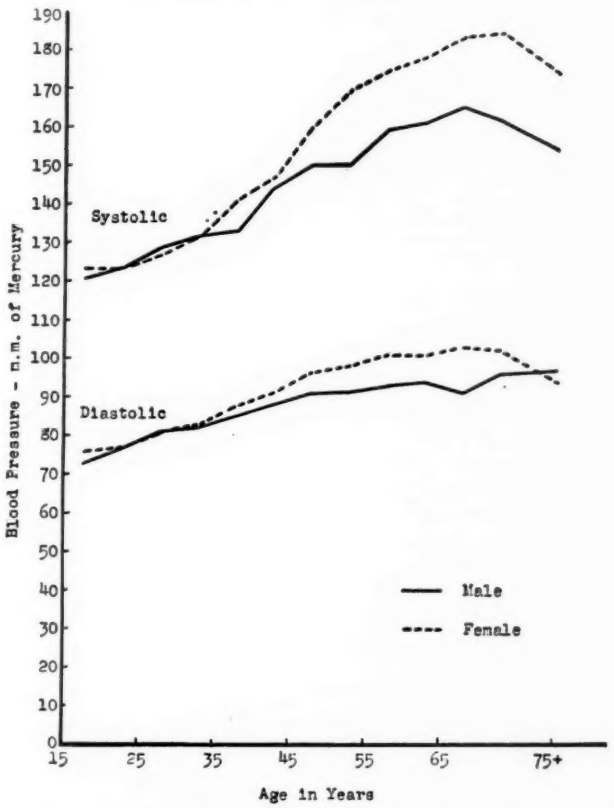

Fig. 1.—Mean systolic and diastolic blood pressure by age in Virgin Islands negroes.

with low blood pressure is large in early life and decreases to a low level in later life, with an excess of "low-pressure" males at all ages. This probably indicates that the mean systolic values which we obtained were not unduly influenced by very high or very low pressures. Considerably more than 50 per cent of all persons between the ages of 15 and 50 years have a systolic blood pressure between 110 mm. and 150 mm., but after the age of 50 years the most common level is above 150 mm.

A special analysis was made of blood pressure in negroes in relation to age and weight. Table IV shows mean systolic blood pressure for

TABLE III

PERCENTAGE OF NEGROES WITH SYSTOLIC BLOOD PRESSURE ABOVE 150 MM., AND BELOW 110 MM., BY SEX AND AGE

AGE (YEARS)	PERCENTAGE ABOVE 150 MM.		PERCENTAGE BELOW 110 MM.		PERCENTAGE 110-150 MM.	
	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES
15-19	5.0	2.2	24.2	17.8	70.8	80.0
20-29	8.4	4.5	18.6	16.4	83.0	79.1
30-39	18.6	17.2	14.6	8.8	66.8	74.0
40-49	41.0	39.1	9.2	2.4	49.8	58.5
50-59	49.6	62.3	4.9	1.0	45.5	36.7
60-69	59.4	73.5	2.9	0.4	37.7	26.1
Over 70	66.7	73.1	4.2	0.0	29.1	27.0

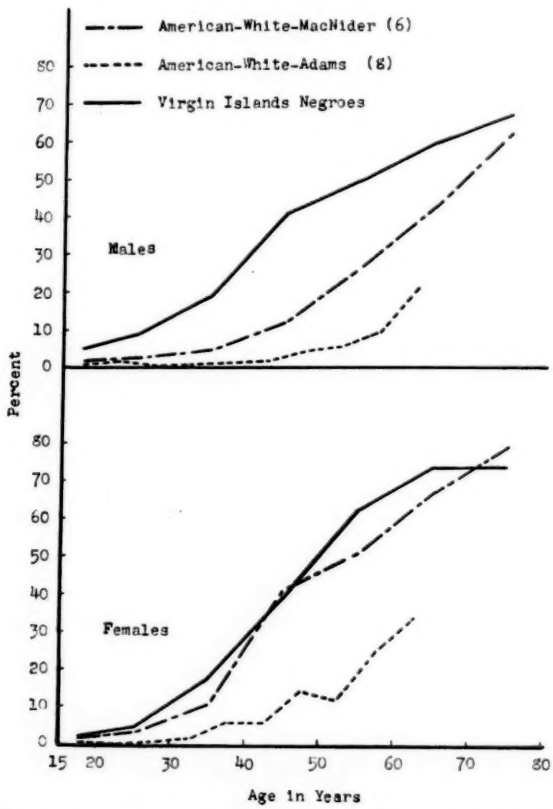

Fig. 2.—Percentage of males and females by age having systolic blood pressure of 150 or more mm. of mercury.

males and females of different weights in many age groups. There was a slight increase in each age group with increasing weight, but the increase in pressure was much more marked with increasing age. Correlations were made for each sex between systolic blood pressure, age, and weight. The correlation coefficient of mean systolic blood pressure with weight, for persons 15 to 69 years old, was 0.1360 ± 0.0241 for

males, and 0.2327 ± 0.0200 for females, which indicates a very low degree of correlation between systolic pressure and weight for both males and females. The correlation coefficient of mean systolic blood pressure with age, for the same age group, was 0.5039 ± 0.0177 for males and 0.7367 ± 0.00934 for females, which represents a fairly high correlation in both sexes. The correlation coefficient for weight with age was 0.0517 ± 0.0245 for males, and 0.2098 ± 0.0202 for females, which indicates no correlation between age and weight in males, but a slight

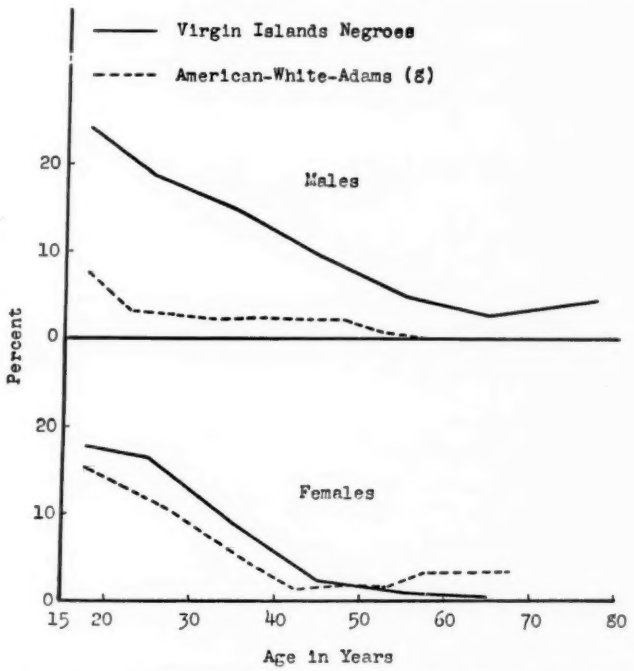

Fig. 3.—Percentage of males and females by age having systolic blood pressure of less than 110 mm. of mercury.

correlation in females. It appears that females tend to gain weight with age, but that males do not. The partial correlation coefficient of mean systolic blood pressure with age, with the weight constant, was 0.5022 for males and 0.7232 for females. The partial correlation coefficient of mean systolic blood pressure with weight, with the age constant, was 0.1281 for males and 0.1182 for females. From these calculations it is apparent that there is a fairly high degree of correlation of systolic blood pressure with increasing age and that this is not due to increasing weight.

Because a considerable proportion of the population was found to have syphilis, it was thought advisable to compare systolic pressure in negroes who had positive serologic reactions with those who had negative reactions. The mean systolic pressure for both males and females with

TABLE IV

MEAN SYSTOLIC BLOOD PRESSURE (IN MILLIMETERS OF MERCURY) OF NEGROES, BY SEX, AGE, AND WEIGHT

AGE (YEARS)	WEIGHT (POUNDS)													
	LESS THAN 100		100-119		120-139		140-159		160-179		180-199		OVER 200	
	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES
15-29	110.7	119.6	116.0	121.9	121.6	124.9	124.7	128.6	129.7	132.1	129.0	131.2	133.3	137.5
30-39	117.5	129.2	121.5	132.8	126.6	136.5	132.0	136.9	133.8	140.9	141.9	132.8	136.1	168.6
40-49	122.5	140.1	139.7	153.1	145.6	149.3	145.1	153.0	151.9	155.5	146.4	158.1	155.0	166.9
50-59	162.5	166.9	136.2	160.5	150.6	171.2	158.4	176.9	159.5	170.0	147.3	187.7	171.1	173.8
60-69	167.5	170.8	161.6	180.5	159.8	181.1	164.8	178.6	156.2	180.0	160.3	172.8	169.6	178.5
15-69	137.5	133.9	128.8	137.1	134.4	144.6	137.8	151.3	141.6	154.5	142.1	155.0	152.7	165.1
No. in Total	9	171	111	641	504	634	613	393	295	209	90	126	40	63

syphilis was appreciably higher than for those without syphilis, but, when the blood pressure was standardized for age, there was no significant difference. This is easily understood because both syphilis and systolic blood pressure increase with age, and the syphilitic subjects represented an older group in which higher blood pressure was to be expected.

TABLE V

MEAN DIASTOLIC BLOOD PRESSURE OF NEGROES, BY SEX AND AGE

AGE (YEARS)	MALES			FEMALES		
	NO.	PRESSURE (MM.)	STANDARD DEVIATION OF SAMPLE	NO.	PRESSURE (MM.)	STANDARD DEVIATION OF SAMPLE
15-19	240	72.45	11.39	315	75.31	10.71
20-24	268	76.40	11.02	287	76.60	11.25
25-29	223	80.65	13.34	275	80.27	11.51
30-34	155	81.80	13.91	214	83.13	14.69
35-39	144	84.35	15.42	216	87.10	16.39
40-44	121	87.60	17.37	216	90.09	15.79
45-49	139	90.30	17.69	209	95.61	16.97
50-54	133	90.70	16.73	220	97.75	17.93
55-59	134	92.20	20.68	199	100.16	18.40
60-64	125	93.50	20.19	142	100.07	16.16
65-69	80	90.20	17.35	100	102.35	26.53
70-74	39	95.30	19.51	67	101.30	15.96
75-79	25	94.90	17.08	40	96.12	17.78
Over 80	17	97.50	25.02	23	88.80	14.63
Total	1,843	84.05	17.25	2,523	88.15	17.82

TABLE VI

MEAN DIASTOLIC BLOOD PRESSURE OF WHITE PERSONS, BY SEX AND AGE

AGE (YEARS)	MALES			FEMALES		
	NO.	PRESSURE (MM.)	STANDARD DEVIATION OF SAMPLE	NO.	PRESSURE (MM.)	STANDARD DEVIATION OF SAMPLE
15-19	39	71.45	9.85	22	73.87	13.38
20-24	39	72.35	9.60	30	74.84	9.38
25-29	33	75.10	10.75	28	75.36	9.10
30-34	36	80.40	12.49	33	77.35	8.65
35-39	37	84.55	11.35	23	80.55	11.21
40-44	29	83.90	9.63	24	79.80	9.35
45-49	20	84.50	12.48	30	82.17	10.08
50-54	24	86.65	12.65	17	86.02	14.11
55-59	17	91.05	17.29	14	95.85	13.82
60-64	7	96.05	17.48	19	85.39	14.99
65-69	8	92.50	16.40			
Over 70				8	95.00	14.74
Total	289	80.55	13.74	249	80.29	12.12

Diastolic Blood Pressure.—The results of our observations on diastolic blood pressure are given in Tables V and VI. These tables show that, in negroes, the pressure in females was significantly higher than in males, and that the pressure in whites was significantly lower than in negroes, with little difference between white males and females. In all groups there was an appreciable increase in pressure with advancing

age, but the rate of increase was less than that for mean systolic pressure. Fig. 1 shows this point graphically; the difference between the curves of systolic and diastolic pressure increases with age, indicating increasing pulse pressure.

DISCUSSION AND COMPARISON WITH OBSERVATIONS ELSEWHERE

There are clear-cut race and sex differences in mean blood pressure in the Virgin Islands. Negroes have a higher systolic and diastolic blood pressure than whites, and, among negroes, females have a higher pressure than males; the sex differences become apparent after the age of 35 years. In negroes there is a significant increase in systolic pressure with advancing age, but weight has little apparent effect. Much has been written about "normal" levels for blood pressure, and it is evident that what might be classed as normal for one population group would be considered as abnormal for another. Virgin Islands negroes have a high "normal" blood pressure as compared with standards in North America. In this discussion, normal is taken to mean that which is usual, regular, or most common, rather than that level of pressure, above or below which there is an excess morbidity and mortality.

Published observations on the average systolic pressure of men and women in the United States have been numerous and varied. We have selected for comparison two main classes: (1) observations upon persons who have been accepted as life insurance risks, and (2) observations upon a random group of persons attending a large clinic in a midwestern city, and upon a random group of private patients in New York City.

Symonds[3] analyzed the blood pressure of persons insured by the Mutual Life Insurance Company between 1907 and 1920. The systolic pressure of 150,000 men ranged from 121 mm. among those who were 15 to 19 years old to 135 mm. among those who were more than 60 years old. The average pressure of 12,000 women increased from 119 mm. to 135.5 mm. during the same life span. Hunter and Rogers[4] discussed blood pressure measurements made between 1913 and 1917 on 62,000 men and 5,000 women who were accepted as life insurance risks. Their observations were in essential agreement with those of Symonds, and showed that the average pressure of men increased from 120 mm. at 15 to 19 years of age to 134 mm. among those who were 55 to 59 years old, whereas the pressure of women increased during the same time from 117 mm. to 134 mm. Symonds' average systolic pressure for males of all ages was 125.3 mm., and, for females, 122.8 mm., which is a significant difference. Another group of life insurance examinees was discussed by Robinson and Brucer,[5] who analyzed measurements on 11,383 persons, all of whom had life insurance policies, and most of whom were urban dwellers of sedentary habits. In this group, 7,478 men showed a range in average pressure from 118 mm. in the 15 to 19 year group to about 134 for those

who were 60 to 69 years old. The average pressure of 3,405 women during the same span increased from 107 mm. to about 147 mm. The average for all men was 121 mm., and, for all women, 117 mm.

In the first two groups, the average systolic pressure was almost identical, age for age, but in the third group the pressure of the men was at a lower level, with a lower mean, and that of the women began at a considerably lower level in the early age groups, but increased to a higher level later, although the mean was considerably lower than for men, and much below that of the first two sets of life insurance figures. Persons who are able to buy life insurance policies are, of course, a highly selected group. In the first place, few of them belong to the lower economic levels, and, in the second place, persons with a known elevation of blood pressure will seldom be granted life insurance policies. Therefore, it is to be expected that mean blood pressure will average lower in such a group than in one which was not selected in this way. By comparison, both negroes and whites in the Virgin Islands had a higher mean systolic blood pressure in all except the younger age groups.

More nearly random groups were presented by MacNider[6] and Schwartz.[7] MacNider analyzed blood pressure measurements in a group of 5,540 persons who were seen in the University of Minnesota Hospital as outpatients or inpatients. They belonged to the lower or lower-middle classes of society and represented residents of both urban and rural areas; they included many who had no medical complaint, and the author felt they could be considered a fair random sample of the population. However, it is very likely that the group was not a true random sample, because it was composed of persons who sought medical advice at a hospital, and, as such, would be expected to include more than its share of ill people, and probably too many people with an abnormally high blood pressure. The systolic pressure of 2,282 men increased from 115.7 mm. among those who were 15 to 19 years old to 146.9 mm. in the 60 to 69 age group, and that of 3,258 women from 117.9 to 163.9 mm. in the same age range. The mean pressure was not given, but from his tables it is calculated as 123.2 mm. for males and 131.7 for females. The range of pressure was greater in this series than in the life insurance groups; both sexes started at lower levels in the younger groups, but rose to higher levels in the older groups; the greater range was among the females. The average for all ages for males was approximately the same as in Symonds'[3] series, but for females it was considerably higher. Schwartz[7] recorded observations on 5,800 private patients who consulted him over a ten-year period prior to 1940. The persons studied were mostly New Yorkers of sedentary habits, and it is probable that the majority had at least average incomes, for they were presumably able to pay for medical care. In this respect they doubtless were economically

better off than MacNider's[6] group, and were less active physically, for nearly all were urbanites, but otherwise they seem to be fairly comparable. In this series the systolic pressure of the men increased from 116.13 mm. between the ages of 11 and 20 years to 138.3 among those who were 61 to 70 years old; the increase among the women during the same span was from 110.78 to 157.61 mm. The ages were not quite comparable to MacNider's,[6] but the average pressure of both the men and women was lower for most ages. The mean, as computed from Schwartz' figures, is about 121.0 mm. for men and 129.0 mm. for women, which is only slightly lower than MacNider's averages. But in both these random series, although the average pressure was considerably higher than in the selected life insurance groups, it was still much lower than in Virgin Islands negroes and whites.

The proportion of Virgin Islands negroes with a systolic blood pressure of more than 150 mm., and the proportion with less than 110 mm., when compared with data from the United States, show marked differences. Adams,[8] using life insurance examiners' figures, showed that among men the percentage with a systolic blood pressure in excess of 150 mm. increased slowly from 0.6 at the ages of 15 to 19 years to 1.8 at 40 to 44 years, and more rapidly, thereafter, to a level of 21.0 at 60 to 64 years. Among females, the proportion was less than 1 per cent up to the age of 35 years, after which there was a steady increase to 33.3 per cent at 60 to 64 years. Among males the proportion below 110 mm. decreased from 7.6 at the ages of 15 to 19 years to zero at 55 years, whereas in females the proportion decreased from 15.3 per cent to about 1.5. MacNider's[6] figures showed a much higher proportion of persons with a systolic blood pressure above 150 mm. at all ages than those of Adams,[8] but were still lower than the Virgin Islands figures. It is apparent from Figs. 2 and 3 that, in Virgin Islands negroes, not only do a greater proportion of persons have a systolic pressure above 150 mm., but also that a greater proportion have pressures below 110 mm.

The mean diastolic pressure of Virgin Islands negroes is considerably higher at all ages than that of Virgin Islands whites, which, in turn, is above the mean in MacNider's[6] random sample in the United States; furthermore, Robinson and Brucer[5] showed that the mean was still lower in their group.

From the foregoing discussion certain things are evident: (1) Virgin Islands negroes have mean systolic and diastolic blood pressures which are much higher than those of persons in the United States; (2) the blood pressure of Virgin Islands whites is slightly higher than that of persons in the United States; (3) in both localities, after middle age, females have a higher blood pressure than males; and (4) a greater proportion of Virgin Islands negroes have both high and low blood pressure than do residents of the United States.

Can these differences be explained on the basis of race, climate, general economic level, or other environmental factors? The racial factor is probably important, because, in the Virgin Islands, the negro and white samples were comparable as to climatic environment, and, although the economic status of the whites may have been a little better than that of the negroes, the difference was not great. It is likely that the great majority of persons in the random samples studied by MacNider[6] and Schwartz[7] in the United States were white, which may explain why their blood pressure was lower than that of Virgin Islands negroes. There is some evidence that, in the United States, negroes have a higher blood pressure than whites. Adams,[9] who studied blood pressure in a group of white and colored workmen in the South, found that the average systolic pressure of 8,000 whites ranged from 117 mm. between the ages of 18 and 20 years to 139 mm. between 61 and 65, and, of 6,000 negroes, from 125 mm. to 148 mm. for the same ages. Dunn[10] stated that hypertensive heart disease occurs more frequently and is more severe in colored than in white women. On the other hand, Crile[11] stated that hypertension rarely occurs among primitive negroes, and Donnison[12] showed that, among 1,000 healthy, adult, male negroes in Kenya, in East Africa, the mean systolic pressure was very low; it increased from 123 mm. at the ages of 15 to 19 years to 126 mm. at 25 to 30 years and then decreased to about 106 mm. at the age of 60 years. Both Crile and Donnison believed that the "primitive" negro has a lower blood pressure than the "civilized" white person because the stress and strain of modern civilization have tended to produce hypertension. However, this is not a very logical explanation for the high blood pressure in the Virgin Islands, where most of the inhabitants are not much troubled by the stress and hurry of modern civilization. On the contrary, although they are poor and lacking in many things, they are, on the whole, quite contented, happy, and carefree. One must conclude that a racial difference actually accounts for higher blood pressure in negroes.

But, in addition to having more high blood pressures, the Virgin Islands negroes have more low blood pressures than the general population in the north. The excess of low blood pressure may be a result of climate and general environment. It is fairly generally agreed that blood pressure is lower in a tropical environment than it is in colder localities. Mason[13] showed that the average systolic blood pressure among white women dropped from 112 mm. to 107 mm. after they moved from a temperate to a tropical climate. Roddis and Cooper[14] showed that the systolic pressure of naval officers who were residing temporarily in the tropics was 10 to 12 mm. lower than would be considered normal in a temperate climate, and they concluded that blood pressure is modified by the effects of climate on physiologic activity. Saunders[15] ascribed the low average blood pressure in Yucatan partly to the tropical climate.

Among the negroes in the Virgin Islands there were many large, well-muscled, active laborers who appeared to be in perfect physical condition, with systolic blood pressures below 100 mm. It would seem, then, that at least two factors are active in determining the blood pressure level in the Virgin Islands, namely, race, which makes for higher pressure in negroes, and climate, which tends to lower pressure in all races.

It is interesting to speculate upon the effect economic factors may have upon blood pressure. The inhabitants of the Virgin Islands are generally poor; they suffer from vitamin deficiencies; and both negroes and whites have higher blood pressures than persons in the United States. In the United States, MacNider's random group had higher blood pressures than Schwartz' patients, who represented a higher economic level. It may be that lack of an adequate vitamin supply, partly as the result of poverty, will cause alterations in the vascular system which tend to increase blood pressure.

It is evident that sex influences blood pressure, for, in all the most nearly random samples, females have higher blood pressure than males. The pressure is about equal in the two sexes, or a little lower in females until they become 40 years old, after which it increases much more rapidly in females than in males, which suggests that a physiologic change at the menopause tends to increase blood pressure.

SUMMARY AND CONCLUSIONS

1. The average blood pressure of Virgin Islands negroes and whites is higher than that of residents of the United States.

2. Negroes had a higher average blood pressure than whites, both in the Virgin Islands and in the United States.

3. The systolic blood pressure of Virgin Islands negroes of both sexes increases significantly with age, but not with body weight.

4. Females have a significantly higher blood pressure than males; this difference becomes increasingly evident after the age of 35 years.

5. A greater percentage of negroes in the Virgin Islands have a systolic blood pressure of more than 150 mm., and of less than 110 mm., than residents of the United States.

6. A tropical climate may exert a depressing effect upon blood pressure.

7. Poverty, with its associated vitamin deficiencies, may tend to raise blood pressure.

We wish to thank the many persons who assisted with the observations discussed in this paper. Dr. Knud Knud-Hansen, commissioner of health for the Virgin Islands, who allowed the studies to be made in the Virgin Islands, gave freely of his own time and advice. Dr. Meredith Hoskins, Chief Municipal Physician of St. Croix, Dr. John Moorhead and Dr. Norman Sloan, formerly municipal physicians in St. Thomas and St. Croix, Dr. Walter Corey, of the United States Public Health Service, and Dr. Ricardo Guinto all gave valuable help during the clinic examinations.

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A NEW TYPE OF ELECTRODE FOR ELECTROCARDIOGRAPHY

SIDNEY SCHERLIS, M.D., AND DEXTER S. LEVY, M.D.
BALTIMORE, MD.

IN THE electrocardiographic or cardioscopic examination of large numbers of patients in dispensary or hospital, considerable time is consumed in attaching and removing the electrodes. A new type of electrode, which has been devised in the outpatient department of the

Fig. 1.—Clips as applied to conventional electrodes.

Johns Hopkins Hospital, may be applied and removed much more rapidly than the usual types. These electrodes are constructed by attaching ordinary bicycle clips to the conventional electrodes by means of a thin metal bridge, as shown in Fig. 1. The clip is so mounted as to permit limited motion of the electrode along the side. A round metal disc, about 1⅜ inches in diameter, is joined to the upper surface of the right arm electrode, thus making it unnecessary to disconnect the wire from the right arm electrode and to connect it again to a chest electrode for chest leads. The right arm electrode is easily slipped off the arm, and the metal disc is applied to the precordium; the reversal of current from left leg to chest is accomplished through the electrocardiograph itself.

From the Cardiographic Laboratory, the Johns Hopkins Hospital and Medical School.
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We have noted no appreciable increase in the tendency of the beam or string of the electrocardiograph to "float" because of the use of dissimilar metals. The electrodes may be used with either string or vacuum tube electrocardiographs.

The electrodes, as described, fit most arms and legs. For patients with small, thin arms and legs, a small sponge rubber pad may be used under the bicycle clips to secure a firmer connection.

Department of Clinical Reports

LEIOMYOMA OF THE PERICARDIUM

Report of a Case

Walter W. Brandes, M.D., J. A. C. Gray, M.D.,
and Norman W. MacLeod, M.D.
New York, N. Y.

PRIMARY tumor of the heart or pericardium is so unusual that reports of cases are desirable and interesting. This communication undertakes to present a case of leiomyoma of the pericardium, which is, as far as can be ascertained, the second such case on record, and also to cite briefly recent similar reports.

The entire field of tumors of the heart was reviewed by Yater,[1] in 1931. At that time he found reference to the following pericardial neoplasms: sarcoma, lipoma, polyp, fibroma, phlebogenous angioma, carcinoma (or endothelioma), teratoma, and neurofibroma. He stated that he himself had seen a cyst.

Since 1931, eighteen additional cases of pericardial tumor have been described; the reports of sixteen of these are available. These include lipoma,[2] neurofibroma,[3] leiomyofibroma,[4] fibroma,[5] angioma,[6] teratoma,[7-9] malignant hemangioblastoma,[10] endothelioma,[11, 12] and sarcoma.[13-17]

Since the clinical manifestations in cases of benign tumor vary little from those of malignant tumors, the two may be considered together. The complaints of eleven of these sixteen patients suggested disease of the heart (dyspnea, pain, fatigue, venous congestion).[2, 3, 8-10, 12, 17] Four patients died suddenly; one was a child under treatment for tuberculosis,[4] and another was an infant with pemphigus.[6]

Data upon physical signs are available in twelve cases. Enlargement of the heart was noted in nine.[2-4, 8-10, 14, 16, 17] Of the remainder, one patient presented signs of pericardial effusion,[12] and one had a pericardial friction rub.[15] Bloody fluid was obtained upon pericardial paracentesis in one case,[10] and bloody fluid upon thoracentesis in another.[16]

Roentgenologic examination was made in eleven cases. Generalized enlargement of the heart was described in four;[2, 4, 10, 17] pericardial

From The Roosevelt Hospital, New York.
Received for publication Oct. 31, 1940.

effusion, in one;[12] and localized or bizarre projections from the cardiac silhouette, in seven.[2, 3, 8, 9, 13, 14, 16]

Electrocardiograms were taken in six cases. One tracing exhibited left axis deviation only.[12] All of the remaining five were definitely abnormal, i.e., four showed nonspecific T-wave changes;[14-17] three showed disturbances of rhythm;[9, 14, 16] and one showed slurring of the QRS complex.[17] No instance of changes similar to those described by Vander Veer and Norris[18] as characteristic of subpericardial myocarditis was observed.

A clinical diagnosis of tumor was made in one case.[13] The validity of this diagnosis must remain open to question, for it is the only case in the group in which no autopsy was performed. The existence of neoplasm within the mediastinum was recognized once.[16]

From the foregoing it will be seen that tumor of the pericardium is rare, that it may either attract attention to itself or cause sudden death, and that roentgenologic abnormalities are the most suggestive evidence of its presence.

REPORT OF CASE

W. M., a white American boy, aged 19 years, was admitted to The Roosevelt Hospital July 1, 1939, at 6 P.M. While playing baseball a short time before, he had been seized with a pain in his chest which he thought was due to indigestion. He located the pain behind the lower half of the sternum. He had gone home and taken rhubarb and soda, but obtained no relief, and therefore had come to the hospital.

He stated that he had been in another hospital about six months previously because of a similar pain and that he had been treated for "pericarditis." Subsequently he had been to a clinic where he was told that he had "something wrong with his heart." About two months before his admission to The Roosevelt Hospital he had had a brief attack of the pain, but this had passed off when he took rhubarb and soda. Aside from these attacks, he said that he had always enjoyed good health.

Physical examination showed a well-developed youth who did not appear to be ill. There was no fever. The blood pressure was 120/95.

The positive signs were confined to the heart. On inspection, a definite systolic impulse was seen in the third left intercostal space, just beyond the sternum. Percussion revealed marked widening of mediastinal dullness to the left in the second and third intercostal spaces. There was a loud systolic murmur at the apex.

There was a moderate polymorphonuclear leucocytosis. A roentgenogram of the chest in the anteroposterior position showed a large, smooth, rounded projection occupying the position of the transverse and descending aorta (Fig. 1).

During the night the patient began to vomit, and this symptom continued obstinately despite hypodermics of codeine. In the morning, except for the vomiting, the picture remained essentially unchanged. Because of loss of fluids, an infusion of 10 per cent glucose in saline was given. It was noted at once that the inflow of the fluid was abnormally slow for the technique employed.

About noon, toward the end of the infusion, the patient began to retch more violently than ever, and became cyanotic, after which he had an epileptiform convulsion which lasted several minutes. The infusion was immediately discontinued.

The situation was now rapidly reappraised, and the following points seemed salient. The arterial blood pressure had fallen to 90/60; the venous pressure was high (witness the slow inflow of the infusion); the area of absolute cardiac dullness equaled that of the relative cardiac dullness; and the femoral pulses were equal. Because of these facts, a diagnosis of acute compression of the heart was made;[19] the weight of the evidence favored sudden effusion as the cause. Rupture of a dissecting aneurysm of the aorta into the sac was considered, in view of the percussion and roentgenographic outlines, but the previous history of pericarditis favored the former hypothesis, and the equality of the femoral pulses seemed evidence against the latter. Since it was apparent that immediate action was essential, pericardial paracentesis was decided upon and carried out forthwith.

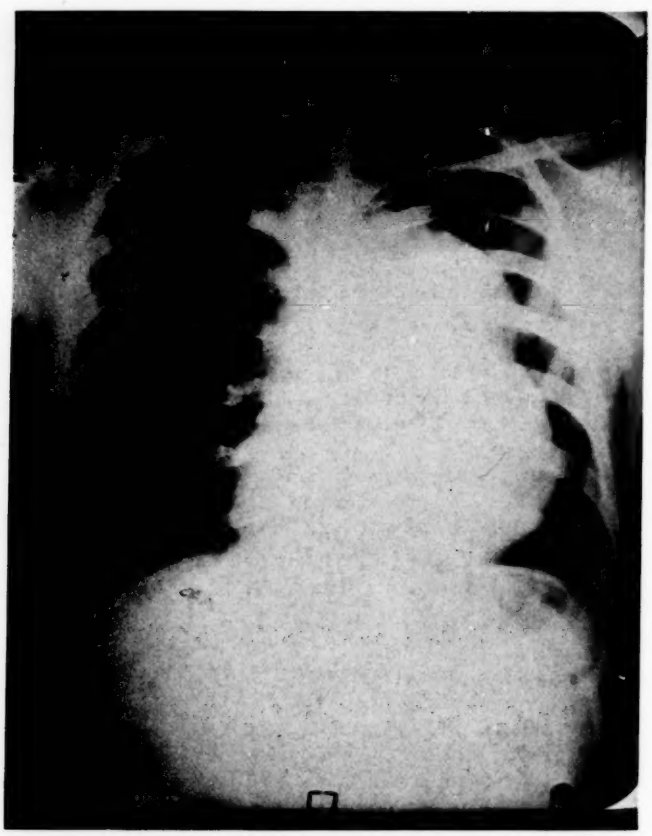

Fig. 1.—Roentgenogram which clearly demonstrates the enlarged heart and bulge of the pericardium, especially over the base.

After the skin was anesthetized with procaine hydrochloride, a needle was inserted into the third left intercostal space within the nipple line and gently introduced to a total depth of 5 cm., constant suction being made. No more than a drop or two of blood was obtained, and no motion of the heart was felt.

At this point, the patient's mother arrived at the hospital for the first time and gave additional information about the case. She stated that she had been told at one of the institutions which he had previously attended that he had "a tumor in his chest," and that he had received roentgen therapy. In the light of

this information the possibility of hemorrhage into a cellular tumor was considered, but, since the patient's condition would not permit taking lateral and oblique roentgenograms, it could not be investigated further. He was given morphine, ouabain, and oxygen on the theory that his one chance lay in conservative management. Despite these measures his cardiac failure became progressively worse, and he died at 6 o'clock the following morning, thirty-six hours after admission to the hospital.

The final clinical diagnosis was dissecting aneurysm of the thoracic aorta.

Fig. 2.—Photograph of the heart with the left ventricle open, exposing aortic valve and mitral leaflet. The tumor is broken up somewhat but is adherent to the parietal pericardium.

Pathologic Observations.—At autopsy, three hours post mortem, there was cyanosis of the skin, conjunctivae, mucosae, and fingernails. Three needle puncture marks were found in the left third intercostal space, 3 cm. to the left of the midline. There were petechiae in the gastric mucosa, generalized venous congestion, and enlargement of the liver.

The pericardial sac measured 15 cm. in width at the base. The apex of the heart was partially obscured on its anterior aspect. In the upper area, over the left auricle and base anteriorly, a definite bulge of the pericardium was evident. This area was tense, and, when incised, allowed the escape of about 60 c.c. of fluid blood which contained shreds of friable, grayish tissue. The parietal pericardium was displaced outward by a large tumor mass in this area (Fig. 2). Over the apex and posterior surface the pericardial space was obliterated by fibrous adhesions, some of which were bloodstained. A line of cleavage could be followed between the tumor mass and the myocardium. The ventricular and auricular muscle was free from involvement on gross inspection. The left auricular cavity

was of small size, apparently because of pressure by the tumor mass. The cusps of the mitral valve were slightly thickened. Their surfaces were smooth. The chordae tendineae were smooth and thin. The endocardial surfaces were smooth throughout. The other valves were not unusual.

Fig. 3.—Photomicrograph of a hematoxylin and eosin stained section of the tumor. Elongated, slender nuclei, with blunt ends are evident. Cytoplasm is faintly visible. (×720.)

Microscopic examination of the tumor revealed uniform-appearing, elongated cells, with long, slender nuclei. Most of the nuclei had blunt ends (Figs. 3 and 4). Some of the nuclei were twisted. The nuclear chromatin was evenly distributed. Nucleoli, when present, were small. A few larger nuclei were dark. Mitotic figures were rarely seen. The cytoplasm was not well stained, but, when seen, was acidophilic. Some cells revealed ribbonlike bands of cytoplasm. The phosphotungstic acid hematoxylin stain revealed no cross striations. The cytoplasm showed bluish, longitudinal streaks, or threads, in some cells, which were suggestive of myofibrillae. The cells were arranged in bundles, coursed in various planes, and were consequently cut at various angles.

The stroma was present in small amounts. Blood vessels were fairly numerous, all of them with well-formed walls. Many of the vessels were dilated and distended with blood. Small hemorrhages were frequent in some areas.

The gross appearance suggested a tumor of the pericardium in which recent hemorrhage had occurred. Older, smaller hemorrhages probably accounted for the fibrous obliteration of the other portions of the pericardial space. Microscopically, the uniformity of the cells, which showed but slight variation in size and shape, and the absence of invasion of the surrounding tissues or the myocardium strongly suggested that this was a benign tumor of the pericardium. The elongated cells, with, at times, wide bands of cytoplasm and elongated nuclei with blunt ends, are evidence that it was a tumor of smooth muscle origin. As such, it might have arisen from blood vessels somewhere in the pericardium, although it was not possible to ascertain the exact point of origin.

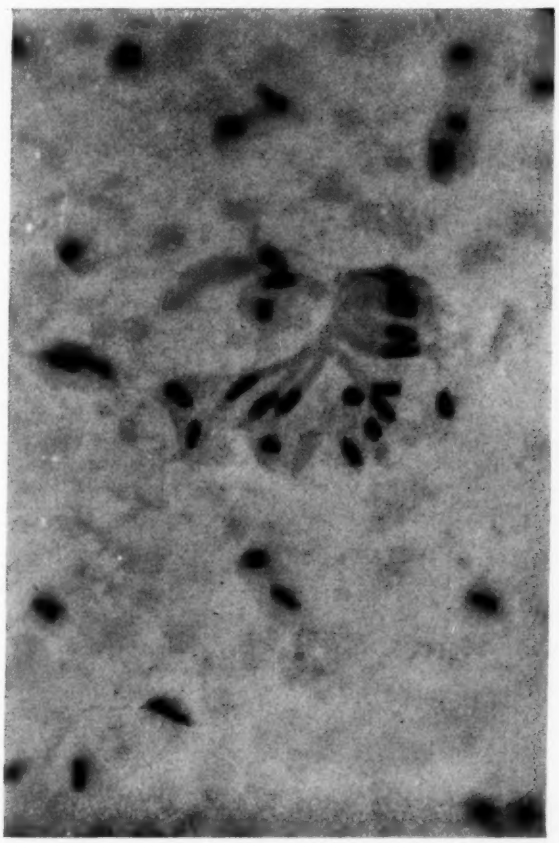

Fig. 4.—Touch preparation of the tumor mass. Rather long, narrow, cytoplasmic bands are clearly demonstrated. (×1500)

COMMENT

Our case appears to be the second recorded instance of leiomyoma of the pericardium; the previous instance was that of Kaplan.[4] The tumor in Kaplan's case was more solid, had a demonstrable origin in the left pulmonic vein, and had not been the site of hemorrhage.

As in the majority of other cases of pericardial tumor, the history, physical signs, and roentgenologic observations attracted attention to the

heart as the site of disease. Like the majority of other observers, we misinterpreted the evidence and arrived at an erroneous diagnosis.

From the pathologic point of view, the cause of death was probably compression of the auricles by the tumor; this compression was suddenly increased by the hemorrhage. Bleeding was doubtless brought on by the patient's exertion when playing baseball.

The case is reported because of its intrinsic interest and as a reminder that, although extremely rare, tumor of the pericardium does occur and should be considered as a diagnostic possibility in the presence of a bizarre clinical picture of heart disease.

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Department of Reviews and Abstracts

Selected Abstracts

Rosenbaum, F. F., and Levine, S. A.: Prognostic Value of Various Clinical and Electrocardiographic Features of Acute Myocardial Infarction: I. Immediate Prognosis. Arch. Int. Med. 68: 913, 1941.

It can be stated that the immediate outlook in a case of acute coronary thrombosis is extremely difficult to predict. Although many of the clinical and electrocardiographic features analyzed may indicate that the condition is either more or less critical, there is practically no criterion which is infallible. However, weighing all the information available together with the general appearance of the patient enables the physician to make a fair estimate as to the immediate prognosis.

AUTHORS.

Hedley, O. F.: Facilities in the United States for the Special Care of Children With Rheumatic Heart Disease. Pub. Health Rep. 56: 2321, 1941.

There were in the United States at the beginning of 1940 one rheumatic heart disease hospital, seven convalescent institutions of various types devoted exclusively to the treatment of children with heart disease, and one organization with a unit furnishing foster home care to children recovering from rheumatic infection. One of the convalescent sanatoriums is adding facilities for the care of essentially hospital cases. Since the beginning of 1940 at least two other rheumatic heart disease sanatoriums have been opened, while beginning in the fall of 1940 a general convalescent institution in Florida was to be devoted entirely to the treatment of rheumatic heart disease.

There are a number of convalescent sanatoriums which furnish care to rheumatic cardiac patients. Although some of them have wards set aside for these patients, in many instances they do not furnish care on a large scale. In most places, additional beds allocated to this purpose would be sufficient.

AUTHOR.

Trotter, W. R., and Eden, K. C.: Total Thyroidectomy for Heart Failure. Brit. Heart J. 3: 200, 1941.

A case has been described in which the complete removal of a normal thyroid gland was followed by the disappearance of auricular fibrillation and congestive cardiac failure. Auricular fibrillation reappeared when the patient was given 1.5 gr. of thyroid extract daily but disappeared again when the dose was reduced to 0.5 gr. daily.

It is suggested that in this case the normal thyroid hormone had the same effect on the heart as has the excessive or abnormal secretion in cases of thyrotoxicosis.

It is suggested that cases of auricular fibrillation or flutter, in which the disorder of rhythm is either paroxysmal or of short duration and in which there is no evidence of structural damage to the heart, might be expected to benefit in a similar way as the result of total thyroidectomy.

AUTHORS.

Baggenstoss, A. H., and Barker, N. W.: Unilateral Renal Atrophy Associated With Hypertension. Arch. Path. 32: 966, 1941.

The incidence of hypertension was determined in eighty-four cases of unilateral renal atrophy and thirteen cases of unilateral renal hypoplasia. There were forty-eight cases of pyelonephritic atrophy, twenty-eight of hydronephrotic atrophy, and eight of pyonephrotic atrophy. Death in most of these cases was due to neoplastic disease or infections of various types. Hypertension was a cause of death in only five cases. Only in the groups of cases of pyelonephritic atrophy (39.6 per cent) and the group of cases of pyonephrotic atrophy (37.5 per cent) was the incidence of hypertension greater than in the control group (29 per cent). The incidence of hypertension was 41.9 per cent for the group of cases of pyelonephritic atrophy in which the atrophied kidney weighed 75 Gm. or less and 35.4 per cent for the group in which the atrophied kidney weighed more than 75 Gm.

In twenty of the forty-eight cases of pyelonephritic atrophy and in twelve of twenty-five cases of hydronephrotic atrophy there was some degree of active inflammation in the opposite kidney. Inflammation in the opposite kidney was present more often in cases in which hypertension was a feature than in those in which it was not observed.

The degree of arteriosclerosis in the opposite nonatrophic kidney was generally less severe than that in the atrophied kidney. In eight of nineteen cases of pyelonephritic atrophy associated with hypertension, the blood vessels were considered normal for the age of the patient.

The results, although of questionable statistical significance because of the small number of cases, suggest that unilateral pyelonephritic atrophy is more often associated with hypertension than would be expected on the basis of chance. They also suggest that hypertension is more likely to be present if the degree of atrophy is severe. As abnormal vascular changes had not occurred in the opposite nonatrophic kidney in a number of cases of unilateral renal atrophy associated with hypertension, it is suggested that in many cases in which hypertension is in an early or mild stage it may not be associated with renal arteriolosclerosis.

AUTHORS.

Oksanen, A. J., Nylander, P. E. A., and Vesa, A.: Concerning the Question of Puerperal Embolism of the Arteries. Acta Soc. med. fenn. duodecim (fasc 3) 27: 1941.

Although embolism of the peripheral arteries, as a disturbance during puerperium, is a most uncommon occurrence, it is not without clinical importance. More often than not diagnosis has been made at a very late stadium, for which reason it is possible that the prognosis of the cases appears to be bad. Operative embolectomy has been performed in a surprisingly small number of these cases and should, in the authors' opinion, be worthy of notice in obstetric circles. The authors describe a case of a 29-year-old woman who, on the fourteenth day after her confinement, which had been accompanied by a puerperal fever, showed symptoms which pointed to embolism of the femoral artery. Large quantities of narcotics were not used, and the embolectomy was performed operatively shortly after. The

operated leg healed completely. When the patient's heart was examined, signs of myocarditis were found, and the authors drew their conclusions from this that the embolus originated from the mitral valve or from some part of the thrombotic matter on the surface of the endocardium of the left side of the heart. The authors analyze the indications for operation and refer to the literature dealing with this subject.

AUTHORS.

Snellman, A.: Contribution to the Clinique of Genuine Basal Cerebroarterial Aneurysms. Acta Soc. med. fenn. duodecim (fasc 3) **27**: 1941.

The author reports eight cases of genuine aneurysm in the region of the anterior portion of the circulus arteriosus willisii, exposed by arteriography and observed by him at the Finnish Red Cross Hospital in Helsinki. In three of these cases aneurysm occurred in the supraclinoid part of the carotis interna, in one case in the arteria communicans anterior (?), in one case in the arteria cerebri anterior, and in three cases in the basal portion of the arteria cerebri media.

From these cases the author believes that it is possible to set up certain clinical types, which are grouped as follows: (1) Apoplectic, violent, lethal cerebral aneurysm; (2) apoplectic, lethal or nonlethal, as well as recidivating cerebral aneurysm (a) with symptoms of abolition from various regions in the cerebral hemisphere or (b) without symptoms of abolition; and (3) cerebral aneurysm with typical or less typical cavernosus syndrome (ophthalmoplegic migraine).

Conservative treatment was used in four of these cases, and surgical therapy, in four. Extracranial carotis ligature was applied in three cases (ophthalmoplegic migraine with aneurysm in the supraclinoid portion of the carotis interna in one case, partial hemiplegia and disturbances of speech with aneurysm in the first part of the arteria cerebri media in one case, and abducens paralysis and aneurysm in the first part of the arteria cerebri anterior in one case. The indication for an application of carotis ligature was different in each one of the cases. The first two mentioned cases recovered without appearance of any cerebral symptoms; in the third case massive hemiplegia and aphasia ensued by the end of the second day, probably as a consequence of secondary thrombosis.

An extensive, subcortical accumulation of blood was removed in one case.

In connection with these cases the author expresses his views on the possibilities of surgical treatment in the aneurysms in question.

The author discusses the etiological viewpoints, and he feels inclined to emphasize the significance of congenital predisposition in some of the cases.

AUTHOR.

Nylander, P. E. A.: Concerning the Question of Thrombosis in the Inferior Vena Cava. Acta Soc. med. fenn. duodecim (fasc 3) **27**: 1941.

The author describes an interesting case of a patient whom he has had under observation for seven years. The patient, a 9-year-old body, was suffering from acute osteomyelitis of the os ilii in which a complication arose in the form of a thrombus in the vena cava. Blocking of the veins led to the formation of a superficial anastomotic network stretching from the upper part of the thigh to the mammary regions, and the superficial veins remained. The child's development continued normally. The action of the heart, at a later examination, was regular; roentgenograms and electrocardiograms showed no deviation from the normal. The author deals briefly with the literature on the subject, taking into consideration the possible indications for operation.

AUTHOR.

Fauteux, M.: Experimental Study of the Surgical Treatment of Coronary Disease Surg., Gynec. & Obst. **71:** 151, 1940.

It has been suggested that the similarity of arteriosclerotic disease of the coronary arteries and of the extremities should permit of the application in the heart of surgical methods found useful in the treatment of peripheral vascular disease. Experiments on dogs are described in which were performed (a) partial coronary arteriectomy of the ramus descendens and (b) partial coronary arteriectomy of the same arterial trunk combined with ligation of the vena cordis magna.

When a partial resection of the ramus descendens at a high level was done, a high mortality resulted. When the same procedure was carried out after venous ligation, all dogs, except those dying of operative complications and intercurrent diseases, remained healthy for more than one year.

It is concluded that vena cordis magna ligation in occlusion of the left ramus descendens helps to maintain adequate coronary circulation after partial coronary arteriectomy.

The results of these experiments suggest that in cases properly selected coronary vein ligation may be expected to act as a preventive measure against a second attack of coronary thrombosis and also to improve the coronary circulation sufficiently to relieve the pain of "angina of effort."

Furthermore it seems a logical procedure in traumatic surgery of the heart whenever it is necessary to ligate an important coronary arterial branch that is bleeding.

AUTHOR.

Atlas, L. N.: The Role of the Second Thoracic Spinal Segment in the Preganglionic Sympathetic Innervation of the Human Hand—Surgical Implications. Ann. Surg. **114:** 456, 1941.

Through a peculiar operative error, an opportunity was presented to perform a controlled study on the contribution of the second thoracic spinal segment in the sympathetic innervation of the human hand. The reported case shows that the second thoracic spinal segment definitely plays an important part in the preganglionic sympathetic innervation of the hand.

Any operation designed to denervate preganglionically the blood vessels of an arm must destroy completely all white rami from the second thoracic spinal segment. In every instance, as determined by skin temperature and sweat distribution studies, complete, immediate denervation of the blood vessels and sweat glands of the upper extremity and the cutaneous vessels and sweat glands of the corresponding half of the face should be obtained. In none should a Horner's syndrome ensue.

AUTHOR.

Gebauer, P. W., and Nichol, A. D. Ligation of the Patent Ductus Arteriosus. Ohio State M. J. **37:** 538, 1941.

Experiences with three cases of patent ductus arteriosus in patients between 11 and 39 years of age are presented. From these patients and from a study of the literature the following tentative conclusions are made.

The authors believe that operation should be performed early because children withstand thoracic surgical procedures so much better than do adults, because the operation is technically easier, and because the shorter the duration of patency the less the degree of pulmonary dilatation, cardiac enlargement, vessel sclerosis, and the less severe the postoperative reaction. Early intervention should be preceded by a period of observation during which diagnostic studies are made, and which is long enough to preclude the rarity of spontaneous closure.

Patients are often urged to lead an inactive life during childhood, may be forced to inactivity by a diminished cardiac reserve in early adulthood, and throughout life are distinctly more susceptible to bacterial endocarditis, aneurysm and rupture of the ductus, or thrombus formation as well as rapid or slow cardiac failure. In some instances, middle life may be reached comfortably. Such instances are rather rare inasmuch as Abbott found the mean age of ninety-two patients to be 24 years at the time of death. On the other hand, the risk of operation is much greater in adults near the limit of their cardiac reserve. The operation may be most difficult because of sclerosis, or because the ductus finally becomes nothing but adjacent holes in the wall of two large vessels. Exploration should be undertaken most cautiously in later life, and in some instances the physician should abandon it rather than attempt to dissect around something which has ceased to exist.

AUTHORS.

Harris, R. I.: Obliterative Vascular Disease: Treatment by Sympathectomy. Canad. M. A. J. **45**: 529, 1941.

The two obliterative vascular diseases commonly observed are Buerger's disease and peripheral arteriosclerosis.

Although the pathologic changes are profoundly different in the two diseases, the result in each case is an intermittently progressive slowing of the circulation which manifests itself by a distinctive clinical picture.

Many cases of either disease have an associated degree of vasospasm which contributes materially to the diminished blood flow. The degree of this vasospasm can be measured by preoperative tests, such as spinal anesthesia and the Landis test.

In all severe cases of Buerger's disease and in selected cases of severe peripheral arteriosclerosis the operation of sympathectomy should be given serious consideration. If the preoperative tests result in a rise in skin temperature of 3° C. or more, a beneficial result from operation can be assured. Even a lower rise in skin temperature does not entirely preclude the possibility of improvement sufficiently great to justify the procedure.

AUTHOR.

Welch, C. E., and Faxon, H. H.: Thrombophlebitis and Pulmonary Embolism. J. A. M. A. **117**: 1502, 1941.

The authors believe that the immediate decision to be made in any given case of thrombophlebitis is whether the patient should be treated conservatively or by ligation of the vein. If conservative therapy is employed, lumbar injection of procaine hydrochloride should be done if vasospasm is considerable. If the deep venous channels are interrupted, heparin is often of value when administered postoperatively. It must be emphasized that these concepts may be modified greatly as our experience increases. The important fact is that thrombophlebitis is no longer observed passively but is now accepted as a disease that must be treated vigorously.

AUTHORS.

Woods, W. W., and Peet, M. M.: The Surgical Treatment of Hypertension. II. Comparison of Mortality Following Operation With That of the Wagener-Keith Medically Treated Control Series. J. A. M. A. **117**: 1508, 1941.

The prognosis of patients with a high level of blood pressure and angiospastic changes of the retinal arterioles is much more favorable following operation than following medical treatment.

The surgical treatment of patients with malignant hypertension has resulted in a survival of 33 per cent after five years, whereas following medical treatment in the control series the mortality was more than 99 per cent.

In general, a favorable prognosis following operation seems to depend on a minimal degree of retinal arteriolar sclerosis rather than on the level of blood pressure, or the absence of retinitis with hemorrhages and exudates, or papilledema.

AUTHORS.

Field, H., Hoobler, S. W., and Avery, N. L.: Results of Chemotherapy in Subacute Bacterial Endocarditis. Am. J. M. Sc. 202: 798, 1941.

Among thirty-six cases of subacute bacterial endocarditis treated with sulfonamide drugs there were five cases with one or more probably falsely negative blood cultures, three instances of probable sterilization of the blood stream with normal temperature temporarily, and one cure of a probably proved case. Among the five patients who also received continuous intravenous infusion of heparin there was one death with cerebral hemorrhage and no cure.

The reported experiences in the chemotherapy of subacute bacterial endocarditis warrant persistence in the accumulation of data concerning the different adjuncts to chemotherapy and the selection of a sulfonamide drug on the basis of bacteriostasis, demonstrable in vitro, for the strain of organism obtained from the individual case.

AUTHORS.

Wilkerson, F.: Functional Cardiac Disorders. J. M. A. Alabama 11: 45, 1941.

The important essentials in the treatment of functional cardiac disorders are, (1) a thorough examination and (2) the proper approach with constantly repeated words of encouragement and reassurance. Faithful following of these ideals will give comfort to a large class of sufferers who, all too frequently, fail to get the help to which they are entitled.

AUTHOR.

Book Review

TREATMENT OF THE PATIENT PAST FIFTY: By Ernst P. Boas, M.D., Assistant Clinical Professor of Medicine, Columbia University. The Year Book Publishers, Inc., Chicago, 1941, 308 pages, 19 illustrations, $4.00.

Nearly half of the pages of this book are devoted to discussion of the cardiovascular diseases. It is apparent that the author is an authority in this field, and it is believed that any practitioner who reads the book would thereby increase his knowledge of heart disease. The material presented is extensive, and considerable space is given to pathologic and diagnostic problems, as well as to treatment. The style of writing tends toward abruptness, with frequent short statements of fact. On debatable points there is a lack of discussion, an omission which may have been purposeful; the author is content to formulate and present his own medical creed. The pages abound in general truths and useful advice, but occasional didactic statements undoubtedly will stimulate the argumentative reader to question whether certain ideas have been established as facts. There is a minimum of references to the literature; this does not detract from the book except when some disputable opinion has been voiced. A few examples of sentences with which the reviewer takes issue are: "Headache suggests the probability of death from apoplexy" (in hypertension). "Potassium sulfocyanate causes such distressing side reactions it should not be used" (in hypertension). "I have a patient who had chancre at the age of twenty and who first developed syphilitic aortitis at age fifty-eight" (syphilitic heart disease). "After the age of sixty, one encounters occasional cases of arteriosclerotic mitral stenosis" (valvular disease). "Airplane flights not exceeding 14,000 feet are not injurious to the heart by reason of the high altitude" (for any continued airplane flight the reviewer believes the oxygen tension is inadequate at more than 10,000 to 12,000 feet for patients who have advanced coronary arteriosclerosis).

It is believed that, although the specialist in the cardiovascular diseases will be disappointed in what he acquires from this book, the general practitioner should find it of some value as a helpful guide in the management of the aging patient. Perhaps certain points which have been mentioned in the book might have been described at greater length, for instance, calcareous aortic stenosis. Arteriosclerosis as a general topic has not been presented in any detail, and this may well reflect realization that there is so much yet to be learned concerning it. The value of salyrgan in the absence of evident edema perhaps has not been adequately discussed. The book much resembles a general synopsis of medicine, and therefore somewhat belies its title. Whether or not the treatment of a patient more than 50 years old is sufficiently different from the treatment of a patient less than 50 years old to justify an entire book on the subject is something about which each physician must form his own opinion.

H. B. BURCHELL.

American Heart Association, Inc.

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

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THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of twenty-seven eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is $5.00. Journal membership at $11.00 includes a year's subscription to the AMERICAN HEART JOURNAL (January-December) and annual membership in the Association. The Journal alone is $10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

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